Identification of Mushroom Lectins and Its Medicinal Properties

G. DHAMODHARAN, S. MIRUNALINI*.

Department of Biochemistry and Biotechnology, Faculty of Science, Annamalai University, Tamil Nadu, India; *mirunasankar@gmail.com*

Summary

This review summarizes the existing information about mushroom lectins. Lectins are abundant in nature like plants, animals, fungi, bacteria and viruses. They are multivalent proteins or glycoproteins of non-immune origin that bind specifically and reversibly to carbohydrates, resulting in agglutination of cells or precipitation of glycoconjugates. The properties of lectins have been known for some time and extensively studied. Their ability to cause disease and to function as markers which delineate specific pathological processes has been reported, but until recently, the role of lectins in the treatment of disease has only been suggested by a variety of sources.

Keywords: lectin, cancer, mushroom, fungi and *Agaricus bisporus.*

***Address for Correspondence:**

Mirunalini Shankaran,
Department of Biochemistry and Biotechnology,
Annamalai University,
Annamalai Nagar-608002,
Tamil Nadu,
India.
Telephone number: 09442424438,
E-mail: mirunasankar@gmail.com

Introduction

The word lectin is from the Latin legere which means "to bind" or to "pick and choose." Lectins were first isolated in 1888 by Stillmark at Estonia University Lectins are found in most plants but are particularly high in legumes and grains (1). Seafood such as shellfish, eel, halibut and flounder also has high lectin contents. The amount of lectin concentration generally accounts for 1% to 3% of the protein content of the specific food, and in the case of plants, the amount is dependent upon the degree of plant maturation (2).

Lectins are non-immunologic protein-polysaccharide molecules having a strong binding affinity for the complex carbohydrates which are abundant on cell surfaces (3). Lectins contain one or more sites specific to carbohydrate binding called Carbohydrate Recognition Domains (CRD) (4,5). Lectins may interact with carbohydrates through hydrogen bonds, metal coordination, Van der Waals, and hydrophobic interactions (6). Basically, hydroxyl groups on sugar molecules can serve as both a donor and an acceptor to cooperate in hydrogen bonds (7).

The binding nature of Lectins is similar to antibodies, forming an irreversible covalent bond. An example of a high molecular weight polysaccharide which conveys a protective effect is arabinogalactan, found in a variety of foods and herbal medicines (8). This class of molecules has been shown to occupy the binding sites of various microorganisms, preventing them from attaching to cellular surfaces and making it easier for the immune system to eliminate them. Lectins are multivalent proteins or glycoproteins of non-immune origin that bind specifically and reversibly to carbohydrates, resulting in agglutination of cells or precipitation of glycoconjugates (9).

Lectins play a crucial role in diverse biological processes, particularly in host defense mechanisms, inflammation, and metastasis (10). Owing to their binding specificities, lectins are employed in a number of biochemical and clinical research areas (11). Lectins are known to cause a number of biological effects including lymphocyte proliferation (blastogenesis) and the induction of cytokine production as well as having the ability to inhibit specific antibody stimulated T cell activity (12).

In recent years, mushroom lectins have become of more interest, mainly due to the discovery of some of these lectins exhibiting potent biological activities. The lectins from

Agaricus bisporus, Ganderma lucidum, Volvariella volvacea, Boletus satanas Lenz, Flammulina velutipes, Lentinus edodes, and Agrocybe cylindracea exhibit potent mitogenic activities (13). In addition, some lectins including mushroom lectins express potential activities such as immunoenhancing, vasorelaxing, hypotensive, and antimicrobial activities (14). *Agaricus bisporus* lectin shows its antiproliferation activity against human colon cancer cell lines HT29 and breast cancer cell lines (MCF-7) (15). *Volvariella volvacea* lectin possesses antitumor activity to sarcoma S-180 cells (16). These clearly indicate that mushroom lectins might be employed as drugs or therapeutic reagents for pharmaceutics. Mushrooms are valuable source of lectins for drug discovery.

Sources of lectin

Lectins are widely distributed in nature, and occur in diverse organisms ranging from fungi, plants, animals, bacteria, and viruses (17).

Fungi

Several fungi can express high levels of saline-soluble and low molecular weight lectins. The parasitic fungus, *Arthrobotrys oligospora*, contains a multi specific lectin that can bind to fetuin and mucins (18). Recently, fungal lectins especially from either mushrooms or filamentous fungi have been the focus of research. The high content of lectins in mushrooms has been detected in diverse species of genera *Lactarius, Russula, Boletus, Phallus, and Hygrophorus. Hemolysins* are found in families *Hygrophoraceae and Strophariaceae*; in genera *Amanita, Mycena, Agrocybe, Oudemansiella, Hebeloma, and Gymnopilus*; and in many ascomycetes (19). Lectins were localized on caps, stipes, and mycelia of mushrooms, and variations in lectin contents occurred upon their carpophore ages and the time and place of harvest (20). Lectins from *Pleurotus cornucopiae* and *Tricholoma mongolicum* have been reported to be isolated from mycelia (21). Surprisingly, the lectin from *Pleurotus cornucopiae* mycelium could be detected only in dikaryotic, not in monokaryotic mycelium, and it disappeared during the formation of fruit bodies (22).

Lectin from Mushroom

Over 2,500 different mushrooms grow in the wild around the world. Mushrooms have been a part of the human diet for thousands of years. They also have been used frequently in homeopathic medicine. Mushroom consumption has been markedly increasing throughout the world and involves a variety of species. Various edible mushrooms are consumed for enjoyment as well as their health benefits such as containing relatively few calories and relatively high amounts of vegetable proteins. Their fruiting bodies, on a dry weight basis, contain about 39.9%carbohydrate, 17.5% protein and 2.9% fats, with the rest consisting of minerals (23).

Mushroom lectins, with an emphasis on those from the following species which have been most extensively characterized including various *Agaricus species, Ganoderma lucidum, Amanita pantherina, Boletus satanas, Coprinus cinereus, Flammulina velutipes, Grifola frondosa, Hericium erinaceum, Ischnoderma resinosum, Lactarius deterrimus, Laetiporus sulphureus, Tricholoma mongolicum and Volvariella volvacea* (24). It is noted that the mushroom lectins exhibit a diversity of chemical characteristics. Some of them are monomeric, whereas others are dimeric, trimeric or tetrameric. Studies on immunomodulatory and antitumour, cytotoxic activities have been carried out on lectins from *Agaricus bisporus, Boletus satanas, Flammulina velutipes, Ganoderma lucidum, Grifola frondosa, Tricholoma mongolicum and Volvariella volvacea* (25).

Molecular structure of mushroom lectin

Lectin is a heterogeneous group of oligomeric protein that varies widely in size, structure, molecular organization, as well as in the constitution of their binding sites (26). Depending on the carbohydrate binding specificity of lectins, affinity chromatography can be effectively used for their purification (27).

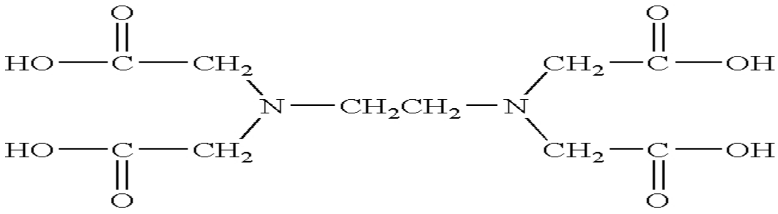

Figure 1: Structure of lectin

Molecular weight and subunits

The molecular weight of mushroom lectins can vary over the range from 13 to 190 kDa. Most lectin molecules are comprised of two or four subunits that may or may not be identical (28). Di-,tri- or tetra- meric lectins from mushrooms with identical subunits have been reported in *Amanita pantherina, Agaricus blazai, Lactarius deterrimus, Ischoderma resinosum, and Hygrophorus hypothejus*. Lectins of *Agaricus edulis, Flammulina veltipes, and Hericium erinaceum* are composed of non-identical subunits (29).

Detection of lectins

Accumulations of lectins in crude extracts of these mushroom specimens were detected by hemagglutination assay using human (A, B, and O blood groups) and animal (goose, rabbit, rat, and sheep) red blood cells. It was found that more than 88% of mushroom extracts predominantly performed hemagglutinating for rat red blood cells (30). The high incidence of lectin accumulations was observed in mushroom specimens belonging to families; *Agaricaceae, Cantharellaceae, Pleurotaceae, and Tricholomataceae.*

Biological activities of lectins

From their carbohydrate specificity, lectins can agglutinate cells, for example, erythrocytes resulting in hemagglutination activities (32). Lectins have been implicated in various biological activities as a result of their recognition of carbohydrates (33).

Cell agglutination

Each lectin molecule, which generally contains two or more carbohydrate binding sites, can interact with cells by combining to sugars on their surface, thus, cross linking the cells and resulting in the phenomena of cell agglutination and their subsequent precipitation (34). So the red blood cell agglutination or hemagglutination of lectins is the major attribute of these proteins, and used routinely for their detection and characterization. Lectins also form cross-links between polysaccharides or glycoprotein molecules in solution, and induce their precipitation reaction (35).

Antiviral activity

Wood et al. (1999) proposed that monocot mannose-binding lectins, e.g. *Liliaceae, Amyryllidaceae, and Orchidaceae* lectins, exhibit anti-retroviral activity. That is possible for applications in crop protection field (36). *Pleurotus ostreatus* lectin (POL) has also been tested for its ability to inhibit HIV-1 reverse transcriptase. No antiviral activity has been displayed but instead POL exerted a powerful antitumour activity (37).

Agaricus Blazei stimulates lymphocyte T-cell and Helper T-cell production. The polysaccharide contained in *Agaricus Blazei* stimulates production of interferon and interleukin that indirectly function to destroy and prevent the proliferation of cancer cells. Also, *Agaricus Blazei* turned out to be a very powerful antiviral agent preventing viruses from entering tissues.

Antibacterial activity

Agaricus bisporus and *Pleurotus sajor* caju have been assayed *in vitro* for their anti-microbial activities using aqueous and organic solvent extracts. It has been shown that Escherichia coli 390, Escherichia coli 739, *Enterobacter aerogenes, Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were most sensitive to aqueous, ethanol, methanol and xylene extracts of these mushrooms (Tambekar et al. 2006).

Antifungal activity

Extracts from fermened broth and mycelium of 15 strains of *Lentinus edodes* have been shown to be active against gram-positive and gram negative bacteria, yeasts and mycelial fungi, including dermatophytes and phytopathogens. The strains differed by the set of the organisms susceptible to the action of the extracts. Strains of *L. edodes* combining marked antibacterial properties and high yields of water soluble polysaccharides were screened. (39, 40)

Phagocytes

Mammalian phagocytes express a wide variety of surface lectins that mediate detection of self and foreign carbohydrates, and these receptors cooperate in detection of microbes. Zymosan is a stimulatory cell wall extract of *Saccharomyces cerevisiae* primarily containing β-glucans as well as other components such as mannans, mannoproteins, and chitin (41, 42).

Mitogenic stimulation of lymphocytes

Fresh fruiting bodies of the wild ascomycete mushroom (*Xylaria hypoxylon*) a lectin with N-terminal sequence resemblance to a part of *Aspergillus oryzae* genome. The lectin exhibited highly potent antiproliferative activity toward tumor cell lines, and exerted a potent anti-mitogenic action on mouse splenocytes. The hemagglutinating activity of the lectin was inhibited by inulin and xylose. The distinctive features of this lectin comprise unique sugar specificity, and highly potent hemagglutinating, antiproliferative and anti-mitogenic activities. *X. hypoxylon* lectin differs in molecular mass, N-terminal sequence and sugar specificity from previously reported ascomycete mushroom lectins.

The hemagglutinating activity of pinto bean lectin was stable within the pH range of 3–12 and the temperature range of 0–70 °C. By using the (3H-methyl)-thymidine incorporation assay, it was shown that the lectin had the ability to evoke a mitogenic response from murine splenocytes but it did not inhibit proliferation of L1210 leukemia cells. The pinto bean lectin inhibited HIV-1 reverse transcriptase.

A novel lectin having specificity towards a complex glycoprotein asialofetuin was purified from tubers of *Arisaema flavum* (Schott.) In Oucterlony's double immunodiffusion, the antisera raised against *A. flavum* lectin showed distinct lines of identity with those of other *araceous* lectins. AFL showed potent mitogenic activity towards BALB/c splenocytes and human lymphocytes in comparison to Con A, a well-known plant mitogen. AFL also showed significant in vitro antiproliferative activity towards J774 and P388D1 murine cancer cell lines. (43,44).

Antiproliferative activity and cytotoxicity

Lectins, in particular mushroom lectins, have recently been shown to be of great interest since they have been reported as potential anticancer reagents that can seek out and stop multiplication of cancer cells (45). For example, *Agaricus bisporus* lectin shows antiproliferation activities against human colon cancer cell lines HT29 and breast cancer cell lines MCF-7. The Galβ1-3GalNAc-binding lectin (ABL) elicits a pronounced dose-dependent decline of 3Hthymidine incorporation to these cancer cells with maximal effects of 87% and 50% for HT29 and MCF-7 respectively at 25 µg/ml in serum free medium (46).

Chenguang ZHAO et al reported the anticancer activity of a novel lectin from the edible mushroom *A. aegerita*. The lectin is active against several kinds of tumour cell lines and significantly inhibits the growth of S-180 cells *in vivo*. It is well known that the antitumour mechanism of lectins may come from their immunomodulatory activity. Determining the detailed mechanism of action of AAL and exploring its toxicity and pharmacokinetics may lead to the development of a novel antitumour drug.

Biocontrolling agents

Since some monocot mannose-binding lectins display the potent host defense activity to bacteria that attack plants and even to insects, it is possible for the application of these plant lectins in crop protection against insects and nematodes (47). Additionally, monocot lectins from bulbs often exhibit anti-retroviral activity that might be investigated as human immunodeficiency virus (HIV) drugs (48).

Cancer diagnosis

Lectins have become a well-established means for understanding varied aspects of cancer and metastasis. Evidence is now emerging that lectins are dynamic contributors to tumor cell recognition (surface markers), cell adhesion and localization, signal transduction across membranes, mitogenic stimulation, and augmentation of host immune defense, cytotoxicity, and apoptosis.

In 1963, Aubb, Burger and others discovered that a plant lectin, wheat germ agglutinin, has selectively agglutinating property to murine tumour cells. It has been revealed that neoplastic cells are differing from normal cells at the glycoconjugates on the cell surface (49, 50).The edible mushroom lectin from *Agaricus bisporus* (ABL) has antiproliferative effects on a range of cell types. This investigation was undertaken to test whether it might have inhibitory activity on Tenon's capsule fibroblasts in *in vitro* models of wound healing and therefore have a use in the modification of scar formation after glaucoma surgery.

Pharmaceutical products

Lectins with well-defined carbohydrate specificities are now available commercially either as free or immobilized proteins on Sepharose for the purification and isolation by affinity chromatography of glycoproteins, glycopeptides, and oligosaccharides, for example; concanavalin A, lentil lectin, pea lectin, *Phaseolus vulgaris, Griffonia simplicifolis, Ricinus communis, and Maackia amurensis* lectins (51).

***Agaricus bisporus* Lectin (ABL)**

Among 50 mushroom lectins, ABL is well documented because *A. bisporus* is the most popular edible mushroom in western cuisines. The lectin from the common mushroom *A. bisporus*, the most popular edible species in western countries, has potent antiproliferative effects on human epithelial cancer cells, without any apparent cytotoxicity (52). This property confers to it an important therapeutic potential as an antineoplastic agent. ABL has antiproliferative effects on a wide range of cell types. ABL caused a dose-dependent inhibition of proliferation and lattice contraction without significant toxicity (53). ABL might be especially useful where subtle modification of healing is needed, as in eye surgery for glaucoma. ABL has reversed the proliferation of colorectal and breast cancer cells in humans (54) The Galb1–3GalNAca (TF antigen)-binding lectin from the common edible mushroom (*Agaricus bisporus*) has a potent anti-proliferative effect without any apparent cytotoxicity.

Discussion

Lectins have been localized on the caps, stipes and mycelia of mushrooms, and variations in lectin content occur depending on the carpophores age and the time and place of harvest. In mushrooms, lectins probably play an important role in dormancy, growth and morphogenesis, morphological changes consequent on parasitic infection and molecular recognition during the early stages of mycorrhization (55). Mushroom lectins and application in taxonomical, embryological and bacteriological studies, study of the modifications in membrane glycoconjugates and cancer formation, cell sorting, sorting of mutant and tumour cells and isolation of membrane and serum glycoconjugates. Guillot and Konska (1977) cited a number of mushroom lectins as examples to illustrate their statement that affinity chromatography, ion exchange chromatography and gel fltration were used in the isolation of lectins. They concluded that mushroom lectins display differences in the number of subunits, molecular weight, carbohydrate content, amino acid composition, isoelectric point, carbohydrate specificity and specificity toward human erythrocytes (56).

The multifarious, potentially exploitable activities which some mushroom lectins including *Agaricus bisporus, Ganoderma lucidum, Flammulina velutipes* and *Volvariella volvacea* express such as mitogenic, immunoenhancing, antiproliferative, antitumour, vasorelaxing and hypotensive activities may be of interest to immunologists, oncologists and cardiologists (57). *A. bisporus* lectin (ABL) inhibits cell proliferation in a wide range of cells without cytotoxicity, suggesting that this lectin might affect a tumor cellular process fundamental to cell division (58). Most of the lectins discussed in this review originate from edible mushrooms. The not-too-infrequent inclusion of mushrooms as a dietary component, and the finding that some lectins retain their biological activity after passage through the gastrointestinal tract, should make research on mushroom lectins appealing to a lot of investigators. Many aspects of mushroom lectin biology merit examination. To mention just one or two, more information pertaining to the physiological role of lectins in mushrooms is necessary. Whether it is related to defence against assault from pathogenic organisms as in the case of plants awaits corroboration (59).

The details of the mechanism of action of mushroom lectins remain to be ascertained. Comparative research has in the past yielded valuable products. This may at least partially explain why lectin research has encompassed organisms across the animal and plant kingdoms. The continuous research on mushroom lectins may uncover information which could be manipulated for the production of pharmaceuticals and nutraceuticals will be processed shortly.

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