THERAPEUTIC PROTEINS AND PEPTIDES FROM EDIBLE AND MEDICINAL MUSHROOMS- REVIEW

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Abstract

Bioactive proteins and peptides were reported from many sources ranging from bacteria to humans. Many of them are having various bioactive characteristics like antibacterial, antifungal, antiparasitic, antihypertensive, antispotential, anticancer etc., Moreover; many antimicrobial peptides employ sophisticated and dynamic mechanisms of action to effect rapid and potent activities consistent with their likely roles in antimicrobial host defense. The molecules exhibit an antimicrobial activity against bacteria, viruses, and eukaryotic pathogens with different specificities and potencies depending on the structure and amino-acid composition of the proteins and peptides. Here we summarize investigations on bioactive proteins and peptides from edible and medicinal mushroom and discuss prospects for therapeutic applications.

Keywords: Peptide antibiotics, antimicrobial, antitumor, antihypertensive, antioxidant.

Introduction

Peptides and therapeutic proteins have been the target of intense research and development in recent years by the pharmaceutical and biotechnology industry [9]. With advances in biotechnology the production of proteins and peptides in commercially available scale is now possible opening an opportunity to treat a disease conditions. There are currently 885 protein based compounds in clinical studies with an extensive market potential for protein based therapies.

The impact on biotechnology products on both the pharmaceutical industries and new therapies can be illustrated by the fact that approximately 30-40% of recent new drug approvals are in the biological category (Antibodies, Proteins, and Peptides).
In traditional Chinese medicine, extracts from many medicinal mushrooms have long been used for a wide range of diseases. Modern scientific & medical studies support many of these claims. The main areas of medicinal studies include anticancer, cholesterol and blood pressure lowering, liver protective, antifibrotic, anti-inflammatory, antidiabetic, antimicrobial activity [Ooi VEC & Liu F., 1999, Wasser SP & weis AL, 1999a, Wasser SP & weis AL, 1999b, Gunde-Cimerman N., 1999, Wasser SP, 2005a, Wasser SP, 2005b].

Bioactive peptides


Some well-known bioactive peptides include glucagon-like peptide-1 (GLP-1) produced in enteroendocrine L cells of the small and large intestine and secreted in a nutrient-dependent manner, which is used for the control of diabetes [Holst JJ, Deacon CF, Vilsboll T, Krarup T, Madsbad S, 2008]. Ghrelin, a 28-amino-acid peptide hormone that is secreted primarily by stomach cells with lesser amounts secreted by other cells (as of the hypothalamus), that is a growth hormone secretagogue, and that has been implicated in the stimulation of fat storage and food intake which is used to treat obesity [Yada T, Dezaki K, Sone H, Koizumi M, Damdindorj B, Nakata M, Kakei M, 2008].

Defensin, a small cysteine-rich cationic proteins found in both vertebrates, invertebrates and plants is used as an antimicrobial agent [Tanabe H, Avabe T, Maemoto A, Ishikawa C, Iniba Y, Sato R et al., 2007].

Recently, the biological activities of antimicrobial peptides have been studied and their roles in protection against infection especially in the local immune system against microbial invasion, has been explored [Brodgen KA, Ackemann M, McCuirray PB Jr, 2003 Shij, Zhang G, Wu H, 1999].

Anti microbial peptides generally have 2-9 excess positive charged amino acids (Arg or Lys). Most peptides have at least 50% hydrophobic amino acid residues and a low proportion of neutral, polar and negatively charged amino acids.

This article reviews therapeutic proteins and peptides from edible and medicinal mushrooms.

**Antimicrobial Peptides**

The antimicrobial peptides are secreted by fungi, plants, invertebrates and vertebrates and protect them from invasion of bacteria, fungi, viruses and other pathogens [Hancock RE, Lehrer RI, 1998, Ganz T, 2003]. The results of studies from the last decade led to the idea that all multicellular organisms possess these forms of non-specific host defense systems and the innate immunity. Antimicrobial peptides have diverse structures and functions and interact with cell membranes of invader cells by disturbing the membrane integrity. This action leads to cell lysis and, later, to their death [Niidome T, Urakawa M, Takaji K, Matsuo Y, Ohmori N, Wada A et al, 1999, Epand R.M, Vogel H.J, 1999].

The investigation of the properties of the antimicrobial peptides is a field of remarkable interest to discover its mechanism of action and develop strategies for new biotechnological applications in medicine and plant protection. The most widely used methods of investigation of the antimicrobial peptide structure are nuclear magnetic resonance (NMR) spectroscopy and X-ray diffraction. The thermodynamic parameters of interactions, the structure and the stability of antimicrobial peptides have not been studied in detail.

Hundreds of peptide antibiotics have been described in the past half-century. These falls into two classes, non-ribosomally synthesized peptides, such as the gramicidins, polymyxins, bacitracins, glycopeptides, etc., and ribosomally synthesized (natural) peptides. The former are often drastically modified and are largely produced by bacteria, whereas the latter are produced by all species of life (including bacteria) as a major component of the natural host defense molecules of these species.[ Hancock R.W, Falla T, Brown M.H, 1995, Kleinkauf H, Von Dohren H, 1998, Perlman D, Bodansky M, 1971].

**Modes Of Action**

Antimicrobial peptides of diverse origin may demonstrate similar modes of action. [37]

**Barrel-Stave Mechanism**

In the barrel-stave model, channel-forming peptides position in a ring is a barrel-like, around an aqueous pore. Peptides or peptide complexes may constitute individual transmembrane spokes in the barrel, and this is the origin of the term "stave" in the model.
Carpet Mechanism

In the carpet mechanism, a high density of peptide acts upon the microbe and causes phospholipids displacement, changes in membrane fluidity, and/or reductions in membrane barrier properties, which lead to membrane disruption. The peptides initially bind to the membrane by electrostatic interactions, yet no quaternary structures are formed. Rather, the membrane integrity is lost after a sufficient concentration of peptides is reached, causing unfavorable membrane energetics. Peptides operating under this model do not form channel-like structures and may not integrate in the hydrophobic membrane core. [Micheal R, Yeaman and Nannette Y Yount, 2003]

Cell Membrane

To disrupt the cell membrane is potentially to disrupt many components of the cell membrane. Functions of cell membrane components include [http://cellbio.utmb.edu/CELLBIO/membrane.htm Accessed February 20, 2009].

- Protection
- Transport regulation
- Signal transduction
- Allow selective receptivity
- Cell recognition
- Provide anchoring sites
- Provide a stable site to bind and catalyze enzymes
- Allow directed cell or organelle motility

Toroid Pore Or Wormhole Mechanism

The intercalation of lipids with peptides is the fundamental difference between the toroid pore mechanism and the barrel-stave mechanisms. The structure created by peptides operating under this mechanism has been called a supramolecular complex, and it includes polar peptide surfaces and phospholipids head groups. After the disintegration of the pore, the peptides translocate to the cytoplasmic leaflet of the membrane. [Micheal R, Yeaman and Nannette Y Yount, 2003]

Advantages Of Mushroom Proteins & Peptides

Mushrooms represent a major and as yet, largely untapped source of potent new pharmaceutical product. Out of approximately 15,000 known species 2,000 are safe for human consumption and about 650 of these possess medicinal properties.

Edible mushrooms once called the “food of the gods” and still treated as a garnish or delicacy can be taken regularly as part of the human diet or be treated as healthy food or as functional food

Some advantages of using mushroom as a source of bioactive compounds are that often the fruiting body can be produced in much less
time, the mycelium may also be rapidly produced in liquid culture that can be manipulated to produce optimal quantities of active products or from mycelia biomass and supernatant of submerged culture using bioreactors [Bose SR, Campestrin, 1955, Hikino H, Ishiyama M, Suzuki Y, Konnoco, 1985, Harttig V, Anke T, Scherer A, Steglich W, Leaiana, 1990, Sarkar S, Koga J, Whitley RJ, Chatterjee S, 1993, Cui J, Chisti Y, 2003]. Mushrooms have a beneficial regulating effect on the immune system [Poucheret P, Fons F, Rapiors, 2006]. It is estimated that 50% of annual 5 million metric tons of cultivated mushrooms contain functional or medicinal properties, which may be utilized as source of biologically and physiologically active substances [Cheung LM, Cheung PCK, Ooi VEC, 2003]. The protein content in mushroom is usually very high in majority of the wild mushrooms, representing 10-44% of dry weight [Longrah T, Deosthale YG, 1998]. They are also proven to be a good source of essential amino acids such as leucine, valine, threonine, lysine, methionine and tryptophan.

Leucine and Valine were found to be the most abundant essential amino acids, comprising 25-40% of the total amino acid content [Chang HL, Chao GR, Chen CC, Mau JL, 2001, Yang JH, Lin HC, Mau JL, 2001, Mdachi SJM, Nkunya MHH, Vitus VA, Nyigo A, Urasa IT, 2004, Guo LQ, Lin JF, Lin JF, 2007]. They are important in providing structure to cells, tissues and organs and therefore essential for growth and repair [Leon-Guzman MF, Silva I, Lopez MG, 1997].

(I) Edible Mushrooms

(A) Russula Paludosa

A peptide named SU2 was identified from the fruiting bodies of *Russula paludosa*. It was in the length of 10 amino acid sequence (KREHGQHCEF) and molecular mass of 4.5 KDa. The SU2 exhibited potent inhibitory activity on HIV-1 reverse transcriptase at the concentration of 1mg/ml, 0.2mg/ml & 0.04mg/ml, the inhibition rate were 99.2%, 89.3% and 41.8% respectively [Wang JH, X & Ng TB, 2007].

(B) Hypsizigus Marmoreus

A novel Ribosome Inactivating Protein (RIP) was identified from the fresh fruiting bodies of *Hypsizigus marmoreus*. A new RIP, named Marmorin was showing a novel N terminal sequence and a molecular mass of 9567 Da. It inhibited the proliferation of hepatoma Hep G2 cells and breast cancer MCF-7 cells, HIV-1 reverse transcriptase activity and translation in the rabbit reticulocyte lysate system with an IC50 of 0.15, 5.30 and 0.7µl respectively [Holst JJ, Deacon CF, Vilsboll T, Krarup T, Madsbad S, 2008].

A novel protein, Hypsin with a molecular weight of 20 KDa, showing antifungal and antiproliferative activity was isolated from the fruiting bodies
of *Hypsizigus marmoreus*. The protein showed antifungal activity against *Mycosphaerella arachidola*, *Physalospora piricola*, *Fusarium oxysporum*, *Botrytis cinerea* with an IC50 of 2.7, 2.5, 14.2, 0.06 µm respectively. It also showed an ribosome inactivating activity in the rabbit reticulocyte lysate system with an IC50 of 7 nm and HIV-1 Reverse transcriptase activity was inhibited with an IC50 of 8 µm. antiproliferative activity against mouse leukemia cells and human leukemia and hepatoma cells was observed. The translation inhibitory activity was retained after heating at 100°C for 10 minutes [Jack H. Wong, HX Wang, TB Ng, 2008].

**(C) Pleurotus Citrinopileatus**

A protein with a molecular weight of approximately 15 KDa was isolated and purified from an edible golden oyster mushroom; *Pleurotus citrinopileatus* showed an immunomodulatory activity. The protein was extracted with 5% (v/v) cold acetic acid in presence of 0.1% (v/v) 2-mercaptoethanol, followed by ammonium sulphate fractionation, DE-52 and mono Q anion-exchange chromatography. PCiP (*Pleurotus citrinopileatus* protein) activated the murine splenocytes and increased the proliferation of splenocytes and interferon and also directly activated murine macrophages and alpha tumor necrosis factor suggesting that it strengthen the innate and adaptive responses of the host [Fuu Sheu, Po-jung Chien, His-kai Wang, Hui-hsin Chang, Yuan-Tay shyu, 2007].

**(D) Pleurotus Eryngii**

An antibacterial and hemolytic monomeric protein, Eryngeolysin with a molecular weight 17KDa was isolated from fresh fruiting bodies of the mushroom, *Pleurotus eryngii*. It was showing an excellent similarity in the N-terminal sequence to ostreolysin (from oyster mushroom) and Agrolysin (from *Agrocybe cylindracea*). It was showing marking cytotoxic activity towards leukemia (LI210) cells in the pH 4-12. It was also active against Bacillus species and inhibited basal as well as Concanavalin A stimulated mitogenic response of Murine splenocytes [Patrick H, K Ngai, TB Ng, 2006].

**(E) Flammulina Velutipes (Winter Mushroom)**

A novel single chained, low molecular weight ribosome inactivating protein, Velutin with a molecular weight of 13.8 KDa was isolated from the fruiting bodies of edible mushroom, *Flammulina velutipes*. It was capable of inhibiting HIV-1 reverse transcriptase and β-glucosidase [Wang H, Ng TB, 2001].

**(F) Calvatia Caelata (Puffball Mushroom)**

A peptide with antiproliferative and antimitogenic activities was isolated from the mosaic puff ball mushroom, *Calvatia caelata*. The molecular weight of the peptide was 8 KDa and it was showing a similar N-terminal sequence to that of ubiquitin. The translation in the cell-free rabbit
reticulocyte lysate system was inhibited by this peptide and the peptide also exhibited N-glycosidase activity. The proliferation of spleen cells was inhibited with an IC50 of about 100nm as indicated by the suppression of methyl-3-H thymidine uptake [Lam YW, Ng TB, Wang HX, 2001].

**G** **Pleurotus Ostreatus** (Oyster Mushroom)

A protein, Lectin with antihepatoma and antisarcoma properties was isolated from the fresh fruiting bodies of *Pleurotus ostreatus*. It was a dimeric protein with a molecular weight of 40KDa & 41KDa respectively. It showed a potent haemagglutinating activity and antitumor activity in mice bearing sarcoma S-180(Swiss Webster Sarcoma180) and hepatoma H-22(hepatocellular carcinoma) [Wang H, Gaoj, g TB, 2000].

The peptide was isolated from the fresh fruiting bodies of oyster mushroom, *Pleurotus ostreatus* with a molecular weight of 9KDa with a novel N-terminal sequence GPCYLVAFYESSGRR. The peptide was isolated by ion exchange chromatography on CM-Sepharose & Mono-S. The peptide was adsorbed on both types of chromatographic media. It showed a ribonuclease activity towards least tRNA with a concentration of 650µl/mg. it also inhibited cell-free translation in a rabbit reticulocyte lysate system with an IC50 of 15nM [Ye XY, Ng TB, 2002].

**H** **Agrocybe Cylindracea**

A peptide showing antiproliferative and ribonuclease activities having N terminal sequence similar to that of ubiquitin and a molecular mass of 9.5 KDa was isolated from *Agrocybe cylindracea*. The peptide showed an antiproliferative activity on leukemia cell line (M1) and hepatoma cell line (HEP G2) and enhanced no production in murine peritoneal macrophages. Also ribonucleolytic activity was preferentially exerted on poly C, lower activity on poly U and RNase activity was stable 0-60°C [Ngai PH, Wang HX, Ng TB, 2003].

An antifungal peptide was isolated from the fresh fruiting bodies of *Agrocybe cylindracea*. *Agrocybin* an antifungal peptide was unadsorbed on DEAE cellulose, and adsorbed on Affi-gel, Blue gel & Mono-S. Its molecular mass was 9KDa and possesses antifungal activity against several fungal species. Also Agrocybin attenuated the HIV-1 reverse transcriptase activity and weakened the mitogenic activity than con A on isolated murine splenocytes [Ngai PH, Zhao Z, Ng TB., 2005].

**I** **Lyophyllum Shimeji**

From the fruiting bodies of *Lyophyllum shimeji* 2 proteins antifungal protein (Lyophyllum) and a ribosome inactivating protein (Lyophyllin) was isolated and their synergic effect was studied.

Lyophyllin, a novel ribosome inactivating protein with molecular weight of 20 KDa, also exhibited antifungal against *Physalospora piricola* (IC50=2.5µm) and *Coprinus cornatus* was isolated. The N terminal sequence
was similar to that of plant RIP (ribosome inactivating protein). It inhibited translation in rabbit reticulocyte lysate with an K50 of 1 µm and HIV-1 reverse transcriptase activity with an K50 of 7.9mm.

Lyophylum, with molecular weight of 14 KDa exerted antifungal activity against *P.piricola* and *Mycosphaerella arachidicola*. It also exerted very low translation inhibitory activity in a rabbit reticulocyte lysate system (K50=70mm). It inhibited HIV-1 reverse transcriptase with a K50 of about 5.2nM and synergism among lyophyllum and lyophyllin against *P.piricola* was also demonstrable [Lam.TB Ng.,2001].

**(J) Clitocybe Sinopica**

A protein with an antibacterial activity was isolated from the dried fruiting bodies of the wild mushroom, *Clitocybe sinopica*. It’s with a molecular weight of 44KDa and composed of 2 subunits. Its N terminal amino acid sequence SVQATVNGDKML was active against *Agrobacterium rhizogenes*, *A.tumefaciens*, *A.vitis*, *Xanthomonas oryzae*, *X.malvacearum* with a MIC of below 0.6µm [Suyue Zheng,Qinghong Liu,Guoqing Zhang,He xiang Wang,Tzi Bun,Ng. ,2010].

**(II) Medicinal Mushrooms**

**(A) Cordyceps Militaris: (Medicinal But Inedible)**

An antifungal protease was purified from dried fruiting bodies of *Cordyceps militaris* with a molecular mass of 12KDa in an optimum condition of 37℃ and at pH 7-9. It showed antifungal effect against *Fusarium oxysporum* and exhibited cytotoxicity against human breast and bladder cancer cells [Byung Tae Park, Kwang Heum Na, Eui Cha Jung, Jae Wan Park, Hah yung Kim,2009].

An antifungal peptide, Cordymin with a molecular mass of 10906 Da was purified from medicinal mushroom *Cordyceps militaris*. The mycelia growth of *Bipolaris maydis*, *Mycosphaerella arachidicola*, *Rhizoctonia solani*Candida albicans was inhibited by the peptide Cordymin with an IC50 of 50µm, 10µm,80µm,0.75µm respectively. The antifungal activity of peptide was stable up to 100℃ & pH range 6-13 and unaffected by Zn2+ and Mg2+. It also inhibited HIV-1 reverse transcriptase with an IC50 of 55. It also displayed anti proliferative activity towards breast cancer cells (MCF -7) [Fernanda Andrade, Nafalda Videira, Domingos Ferreira, Bruno Sarmento,2011].

**(B) Ganoderma Resinaceum, Russula Fragilis And Inocybe Grammata: (Medicinal But Inedible)**

*Ganoderma resinaceum*, *Russula fragilis*, *Inocybe grammata*, *Mycena pura* protein extracts of mushroom were investigated for the potent antimicrobial effects by Kirby Bauer disc diffusion method. The wild type fungus *Mycena pura* exhibited strong antagonism against *E.coli*, effective against Multi Resistant *Staphylococcus aureus*, *Salmonella*, *Candida*, and...
Aspergillus [Micheal Hearst, David Nelson, Graham McCollum, Linda M, Ballard, B. Cherie Millar et al., 2010].

(C) Pleurotus Nebrodensis: (Medicinal But Inedible)

A monomeric protein (hemolysin) with a molecular weight of ~27 KDa was isolated from the edible mushroom Pleurotus nebrodeolysin. It exhibited remarkable hemolytic activity towards rabbit erythrocytes and strong cytotoxicity against Lu-04, Bre-04, HepG2, L929 & HeLa cells. It also possesses anti-HIV activity in CEM cell culture [Hui Lv, Yang Kong, Qing Yao, Bo Zhang, Fang Wei Leng, He jiao et al., 2009].

(D) Ganoderma Lucidum: (Medicinal)

The antioxidant activity by different oxidation system was evaluated in Ganoderma lucidum Peptide (GLP). The strong antioxidant activity was observed in light proof soybean oil, assessed by lipid peroxidant value. The lipooxygenase activity of GLP in soybean was blocked in a dose-dependent manner with an IC50 value of 27.1 mg/ml. The scavenging activity was also observed in hydroxyl radicals with IC50 value of 25 mg/ml. GLP showed an excellent antioxidant activity in the rat liver tissue homogenates and mitochondrial membrane peroxidation systems [Jie Sun, Hui He, Bi Jun Xie, 2004].

A peptide from the mushroom Ganoderma lucidum was assessed for the hepatoprotective activity in mice. The hepatic damage was induced by D-galactosamine (D-Gal N) was manifested by a significant increase in the marker enzyme (ASP, ALT) in serum and liver MDA levels. Also there was a decrease in the activity of Super Oxide Dismutase (SOD), Glutathione Stimulating Hormone (GSH) in liver. However the mice which were pretreated by GLP (Ganoderma lucidum protein) reversed these values to normal. At a dosage of 180 mg/kg, GLP showed an excellent hepatoprotective activity and it was evidenced by biochemical values and liver histopathology [Yanling shi, Jie sun, Hui He, Hui Gun, Sheng Zhang, 2008].

An immunomodulatory protein, LZ-8 from Ganoderma lucidum was proposed to have therapeutic effects on cancer and autoimmune diseases. An efficient and facile expression system supplying of RLZ-8 of high purity and stable activity was developed for further study and applications, a full length cDNA of IZ8 gene was cloned into the pPIC9K to construct a yeast expression vector. pPIC9K–IZ8, then transformed to Pichia pastoris strain GS115. In vitro, the RLZ-8 was capable of haemagglutinating mouse RBCs [Xue Q, Dingy, Shang C, Jiang C, Hao M., 2008].

(III) Edible & Medicinal Mushrooms:

(A) Calvatia Lilacina, Pleurotus Ostreatus & Volvariella Volvacea:

The efficacy against human colorectal adenocarcinoma cells & human monocytic leukemia cells was exhibited with the protein extracts of
Calvatia lilacina, Pleurotus ostreatus & Volvariella volvacea. The protein extract of Pleurotus ostreatus also induced apoptosis in SW480 cells partially through Reactive Oxygen Species (ROS) production, Glutathione depletion (GSH) & mitochondrial dysfunction. So the protein extracts of these mushrooms can be considered as a source of anti cancer drugs [-Yi Wu, Chi-Hung Chen, Wen-Huei Chang, King-Thom Chung, Yi-wen Liu, Fung-Jou Lu, 2011].

(B) Grifola Frondosa (Maitake Mushroom):
A protein showing anti Herpes simplex virus type-1 (HSV-1) activity was purified from the fruiting bodies of Grifola frondosa. The molecular weight was 29.5 KDa and its N-terminal has 11 amino acids.

NH(2)-REQDNAPCGLN-COOH
The replication of Herpes simplex virus type-1 (HSV-1) was inhibited in in vitro condition with an IC50 value of 4.1 mg/ml. The severity of HSV-1 induced blepharitis, neovascularization and Stomal keratitis was reduced by high concentration of GFAHP (125&500 mg/ml) in murine model. The peptide directly inactivates HSV-1 while simultaneously inhibiting HSV-1 penetration into Vero cells [Gu CQ, Li JW, Chao F, Jin M, Wang XW, Shen ZQ, 2007].

(C) Tricholoma Gigantum & Pholiota Adiposa:
A novel antihypertensive Angiotensin I converting enzyme (ACE) inhibitory peptides was extracted and characterized from Tricholoma gigantum & Pholiota adiposa. The fruiting body of Tricholoma gigantum was extracted with distilled water at 30°C for 3 hours and the maximum ACE inhibitory activity was obtained at IC50 of 0.31mg. The peptide was characterized as a tripeptide Gly-Glu-Pro. The water extracts of Pholiota adipose AS124012 fruiting bodies showed potential ACE inhibitory activity of 66% [Dae Hyoung Lee, Kyo Chul Koo, Jeong sik park, Jong Soo Lee, Fifth International conference of mushroom biology and mushroom products].

Conclusion
Mushroom as compared with fruits and vegetables is a better source of protein. The above review focuses on the therapeutic proteins and peptides from edible and medicinal mushrooms which is having antimicrobial, anticancer, antihepatoma etc. characteristics. When an extensive research is carried out, the naturally occurring therapeutic proteins and peptides can be converted into innovative antibiotic drugs.

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