

# Medicinal Properties of Substances Occurring in Higher Basidiomycetes Mushrooms: Current Perspectives

International Journal of Medicinal Mushrooms, Vol 1, 47-50, (1999)

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## CARDIOVASCULAR AND HYPERCHOLESTEROLEMIA EFFECTS

The major cause of death in the Western countries is coronary artery disease. A primary risk factor is hypercholesterolemia, which contributes to hardening of the arteries. In humans, 50% or more of the total cholesterol is derived from *de novo* synthesis (Rosenfeld, 1989; Steinberg et al., 1989). Clinical intervention studies have demonstrated the therapeutic importance of correcting the hypercholesterolemia. The initial step in lowering cholesterol is a special diet low in fat and saturated fatty acids and rich in crude fibers.

Drug therapy is the next step. The best-known pharmacologic agent that was approved in 1987 is lovastatin (mevinolin) and its analogues (Endo, 1988). This low molecular weight substance is the competitive inhibitor of HMG Co A reductase, the key enzyme in cholesterol metabolism that catalyzes the reduction of HMG CoA into mevalonate.

The best known organisms for potential producers of lovastatin from edible higher Basidiomycetes mushrooms are species of the genus *Pleurotus* (Gunde-Cimerman et al., 1993a,b; Gunde-Cimerman and Cimerman, 1995). The presence of the inhibitor was determined in four species: *P. ostreatus*, *P. cornucopiae*, *P. eryngii*, and *P. sapidus*. The highest content of lovastatin was found in the fruiting bodies of the *P. ostreatus*. The appearance of the inhibitor during the development of the fruiting bodies was found in the vegetative mycelium, in the primordial, and in different parts of fruiting bodies of different

sizes; less lovastatin was found in stipes when compared with pileus (fig. 5) or in nature stages in the lamellae and basidioiospores (Gund-Cimerman and Cimerman, 1995)

It was shown that lovastatin at the beginning of mushroom growth is unfortunately distributed in small fruit bodies, and there are no substantial differences between the pileus and the stipe. During fruit body growth, the majority of lovastatin is first transferred to the pileus and later the lamellae. Mature fruiting bodies have a diameter of approximately 15 cm and disperse large amounts of basidiospores. These contain less lovastatin in the lamellae when compared with the smaller, 10 cm diameter; less mature mushrooms this transfer is still incomplete (Gunde-Cimerman and cimerman, 1995).

In a series of experiments conducted by Bobek et al. (1991a,b, 1993), it has been found that the addition of 2% to 4% of *P. ostreatus* to the hyperlipidemic diet efficiently prevented accumulation of C and triacyl-glycerols in both sera and livers of animals with exogenous, endogenous, or genetically induced hyperlipidemia. VLDL cholesterol had the dominant role in the reduction of serum C up to 80% induced by the whole mushroom pr its water and 30% of ethanol extracts. The authors attributed this effect to the fiber pulp complex of the oyster mushroom, which limits the resorption of C and gastrointestinal tract, and to an undefined substance which influences, as well, metabolisms outside the phase of resorption. (Bobek et al., 1991a,b, 1993). Ryong et al. (1989) have tested alcohol and water extracts of 20 different edible mushrooms in tissue primary culture of cells isolated from atherosclerotic action. Four mushrooms also decreased atherogenic effects by 20% to 40% in sera collected from coronary heart disease patients. In these experiments the effect of dietary fibers was excluded and the efficiency was attributed to an unknown active component (Ryong et al., 1989). Authors suggest that this unknown substance is lovastatin, which can be found in

high quantities in the fruiting bodies of various cultured *Pleurotus* species. Therefore, mature fruiting bodies of *P. ostreatus* could be recommended for consumption as a natural cholesterol-lowering agent. Lovastatin appears early in the life cycle of the mushroom, in the mycelia from which primordial are being formed.

It is known that *Lentinus edodes* is able to lower BSC via a factor known as eritadenine (also known as “Lentinacin” or “Lentysine”) was isolated from an 80% ethanol extract of Shiitake mushroom fruiting bodies by absorption on a Amberlite IR-120 (H+) column, followed by elution with 4% NH<sub>4</sub> OH (chibata et al., 1969). A crystalline product had the following properties: mp 261-263° C, C<sub>9</sub>H<sub>11</sub>O<sub>4</sub>N<sub>5</sub>, MW 253,  $\lambda$  261.5 nm (E=14,508)m, Nasapt mp 266–268 C (decomposition),  $\alpha$  D + 45.5 (C=1, H<sub>2</sub>O). Hydrolyses in 6N HCl at 110 C for 72h yielded glycine and new amino acid. Eritadenine apparently reduces serum cholesterol in mice. Its action is not inhibition of cholesterol biosynthesis, but rather the acceleration of excretion of ingested cholesterol and its metabolic decompositions (Makita et al., 1972, cited in Mizuno, 1995a,b).

Apparently, Eritadenine reduces BSC in mice, not by the inhibition of cholesterol biosynthesis but by the acceleration of the excretion of ingested cholesterol and its metabolic decomposition (S. Suzuki and Oshima, 1974, 1976; Higushi et al., 1978; Yagishita et al., 1977, 1978). Eritadenine has been shown to lower blood levels of cholesterol and lipids in animals (Yamamura and Cochran, 1976) Added to the diet of rats, Eritadenine (0.005%) caused a 25% decrease in total cholesterol in as little as one week (Chibata et al., 1969) The cholesterol-lowering activity of this substance is more pronounced in rats fed a high fat diet than those on a low-fat diet (Rokujo et al., 1969). Although feeding studies with humans have indicated a similar effect, further systematic research is needed. S. Suzuki and Ohshima

(1974, 1976) have shown that dietary shiitake mushroom lowered BSC levels. Various studies have confirmed (Kimoto et al., 1976; Kabir and Kimura, 1989) that shiitake mushroom can lower both blood pressure and free cholesterol in plasma, as well as accelerate accumulation of lipids in the liver, by removing them from circulation.

Nucleic acid compound in *L. edodes* extract have been shown a strong platelet agglutination inhibitive effect (antithrombotic activity). An extract of *L. edodes* with antithrombotic activity was studied by high-performance liquid chromatography (HPLC). ATP, ADP, UDPG, 5'-GMP, 5'UMP, 5'-CMP, 5'-AMP, uridine, eritadenine, and deoxylentinacin were identified. More antithrombotic activity was shown by 5'-AMP, 5'GMP, eritadenine, and deoxylentinacin (Hokama and Hokama, 1981; Kabir and Kimura, 1989).

*Auricularia auricula-judae* has shown the following effects and activities in studies on mice and rats: anticoagulation, lowered total cholesterol, triglyceride, and lipid levels (Chen, 1989; Sheng and Chen, 1990); and antiaggregatory activity on blood platelets, which might make it beneficial for coronary heart disease (Agarwal et al., 1982). This mushroom is traditionally used as an immune tonic.

*Tremella fuciformis* polysaccharides and spore extracts have demonstrated antilipemic activity. *T. fuciformis* lowered the LDL- cholesterol in rats fed the preparation, which also contained butter sugar, and egg yolks, by 30% over controls (Nakajima, et al., 1989). *T. fuciformis* polysaccharides prolonged thrombus formation, reduced thrombus size, reduced blood platelet adherence, blood viscosity, and positively influenced other blood coagulation parameters of survival in mice (Sheng and Chen, 1990).

Animal studies on *Armillariella mellea* demonstrated that it decreases heart rate, reduces peripheral and coronary vascular resistance, and increases cerebral blood flow (Chang and But, 1986). AMG-1-a compound isolated from this mushroom exhibits a cerebral-protective effect (Watanabe et al., 1990), and increases coronary oxygen efficiency without altering blood pressure (Y. Zhang et al., 1985)

*Grifola frondosa* reduced blood pressure in rats without changing plasma HDL levels (Kyoto et al., 1988). Adachi and coworkers (1988) found a blood pressure lowering effect with the powder of *G. frondosa* fed to hypertensive rats in their normal food. The effect was of rapid onset, short lived and dose dependent. An aqueous extract of *G. frondosa* also reduced serum cholesterol levels in rats (Mizuno, 1977).

A glycoprotein obtained from submerged cultured mycelial biomass of *Trametes sp.* showed activity (in animal and in vitro test). Against experimental hypertension and thrombosis. The protein inhibits blood platelet aggregation and is antihyperlipemic and antiarrhythmic. (Ikuzawa, 1985) *Trametes versicolor* has been shown to lower serum cholesterol in animals (Yagishita et al., 1977). PKS ( beta-glucan protein) from *T. versicolor* has been used in clinical studies. Tsukagoshi et al (1984) have reported that PSK causes a significant decrease in LDL cholesterol in hyperlipidemia (stage 11a ) patients.

The *Volvariella volvacea* cardioactive proteins are know to lower blood pressure (Cochran, 1978; Yao et al., 1998).