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Hypolipidemic Effects of Biopolymers Extracted from Culture Broth, Mycelia, and Fruiting Bodies of *Auricularia auricula-judae* in Dietary-induced Hyperlipidemic Rats

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Hypolipidemic effect of biopolymers extracted from culture broth (CP), mycelia (MP), and fruiting bodies (FP) of *Auricularia auricula-judae* was investigated in dietary-induced hyperlipidemic rats. The experimental animals were administrated (100 mg/kg body weight) with different biopolymers, daily for 4 weeks. Hypolipidemic effects were achieved in all the experimental groups, however, FP was proved to be the most potent one. The administration of the FP reduced the plasma triglyceride, total cholesterol, low-density lipoprotein cholesterol, and atherogenic index by 24.3, 28.5, 36.4, and 40.9%, respectively, while increased the high-density lipoprotein cholesterol level (9.0%), when compared to the saline (control) administered group.

KEYWORDS: ***Auricularia auricula-judae*, Biopolymer, Hypolipidemic effect**

Hyperlipidemia (mainly increased level of cholesterol or low density lipoprotein cholesterol) is an important risk factor in the initiation and progression of atherosclerotic lesions (Goldstein *et al.*, 1973; Harrison *et al.*, 2003). The beneficial effect of lowering elevated serum cholesterol level in the prevention of coronary heart disease is well established (Lipid Research Clinics Program, 1984; Simons, 2002). Several dietary fibers significantly decrease serum cholesterol and, thereby, reduce the risk for coronary heart disease. The search for natural substances are capable of lowering blood cholesterol is ongoing in the field of nutrition and many of dietary factors, which include plant proteins, unsaturated fatty acids, calcium and flavonoids, have been reported for their hypolipidemic potential (Kang and Song, 1997).

Edible mushrooms are the ideal dietetic materials for the prevention of atherosclerosis due to their high content of fiber, proteins, microelements and their low fat content (Bae *et al.*, 2000; Crisan and Sands, 1978; Kurasawa *et al.*, 1982). *Auricularia auricular-judae* is known to have potent hypocholesterolemic effect in plasma (Kaneda and Tokuda, 1966). The fruiting bodies of *A. auricula-judae* have long been used in food and for medicinal purposes. The polymer of this mushroom also has various biological activities: such as anti-tumor (Misaki *et al.*, 1981), hypoglycemic (Yuan *et al.*, 1998), anticoagulant (Yoon *et al.*, 2003), and anti-complement activity (Jeong *et al.*, 2004).

In the present investigation, hypolipidemic effects of biopolymers extracted from CP, MP, and FP of *A. auricula-judae* in dietary-induced hyperlipidemic rats have been reported.

Materials and Methods

Strains and preparation of CP, MP and FP. *A. auricula-judae* was obtained from the Rural Development Administration in South Korea, while the fruiting body of this mushroom was obtained from the local market. The experimental organism was maintained on potato dextrose agar (PDA, Difco) slant at 4°C and subcultured in every 3 months. The seed culture was grown (25°C/130 rpm/approx. 7 d) in 250-*ml* Erlenmeyer flasks containing 100-*ml* of potato dextrose broth (pH 5.0) medium. One hundred *ml* of the medium with mycelial pellets was then homogenized aseptically in a Sorvall omni-mixer for 3 min in an ice bath (Song *et al.*, 1998) and inoculated in the fermentation media (4%, v/v) for submerged cultivation. The mushroom complete medium (MCM) of the following composition (g/*l*): Glucose 20, $MgSO_4 \cdot 7H_2O$ 0.5, KH_2PO_4 0.46, K_2HPO_4 1.0, yeast extract 2.0, and peptone 2.0, with pH 5.0 was used to perform submerged mycelia culture for the production of biopolymers.

The submerged mycelia cultures were carried out in 500-*ml* Erlenmeyer flasks containing 250-*ml* of MCM media on a rotary shaker (130 rpm/pH 5/25°C). The recov-

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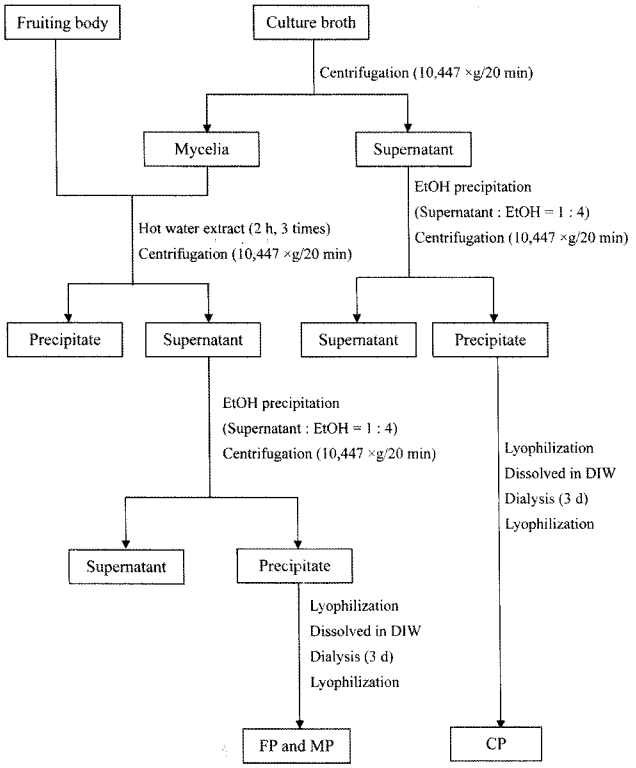

Fig. 1. A schematic diagram depicting the recovery process of biopolymers extracted from culture broth (CP), mycelia (MP), and fruiting bodies (FP) of *Auricularia auricula-judae*.

ery procedure of the CP, MP, and FP of *A. auricula-judae* is shown in Fig. 1.

Animal experiments. Sprague-Dawley male rats (80~100 g) obtained from Daehan Biolink Co., Ltd. (Seoul, Korea) were housed individually in stainless steel cages in a room with controlled temperature (22 ± 2°C), humidity (55 ± 5%), and a 12 h cycle of light and dark. The rats were fed with a modified AIN-76 (American Institute of Nutrition, 1977) high fat diet for six weeks (Table 1).

The animals were provided daily with the diets and water. After two weeks of acclimatization in the growth room, they were brought into the experimental conditions. Based on their body weights, the rats were divided into four experimental group of nine. Each group of nine

Table 1. Composition of high fat diet

Ingredient	Composition (%)
Casein	20.0
Corn starch	34.8
Sucrose	20.0
Cellulose	5.0
DL-methionine	0.2
Vitamin mix*	1.0
Mineral mix*	3.5
Lard	10.0
Corn oil	5.0
Cholesterol	0.5

*Mineral and vitamin (g/kg) mixture (AIN-76).

dietary-induced hyperlipidemic rats was orally administered either with 0.9% saline (control) or CP, MP and FP (100 mg/kg BW: body weight) daily for 4 weeks (Table 2).

The food intake and body weights were recorded every alternate and every day, respectively. At the end of the 4 weeks experiment, the rats were fasted for 12 h and immediately sacrificed, following an abdominal incision under light ether anesthesia. Later, the blood was collected from the main artery into heparinized tubes. Plasma was prepared by centrifugation (1,110×g, 10 min) after keeping the samples at room temperature for 2 h.

Chemical analysis. The level of triglyceride, total cholesterol, and high-density lipoprotein (HDL) cholesterol in plasma were determined enzymatically using commercial kits (Asan Pharm. Co., Ltd., Chungnam, Korea) based on the methods of glycerol kinase (Bucolo and David, 1973), cholesterol oxidase-DAOS (Allain *et al.*, 1974), and phosphotungstic acid-Mg^{2+} precipitation (Finley *et al.*, 1978), respectively. Low-density lipoprotein (LDL) cholesterol and atherogenic index of plasma were calculated by the following equation: LDL cholesterol = total cholesterol – HDL cholesterol – (triglyceride/5) (Friedewald *et al.*, 1972), Atherogenic index = (total cholesterol – HDL cholesterol)/HDL cholesterol (Haglund *et al.*, 1991).

Statistical analysis. Each data value is expressed as the mean ± S.E. The group means were compared using a one-way analysis of variance and Duncan's multiple-range test (Duncan, 1957). The statistical differences were con-

Table 2. Experimental group for identifying hypolipidemic activity

Group	Oral administration
Control	0.9% NaCl
CP	Biopolymer obtained from culture broth of *Auricularia auricula-judae*
MP	Biopolymer obtained from mycelia of *Auricularia auricula-judae*
FP	Biopolymer obtained from fruiting bodies of *Auricularia auricula-judae*

Group of 9 hyperlipidemic rats. The rats in each experimental group were orally administered with either saline (control), CP, MP, and FP at 100 mg/kg body weight daily for 4 weeks.

sidered significant at $p < 0.05$.

Results and Discussion

Growth response. The CP, MP, and FP of *A. auricula-judae* were orally administered to dietary-induced hyperlipidemic rats, daily for 4 weeks. All the biopolymers tested, FP group significantly reduced body weight gain, while, there was no significant effect on food intake and food efficiency ratio in the all experimental group (Table 3). The reduction of body weight observed in the present investigation clearly shows the hypolipidemic potential of FP. The increased body weight observed in hyperlipidemic rats (control group) may be due to accumulation of an excess amount of lipid in the liver tissues (Gurr and Harwood, 1991). The oral administration of CP, MP and FP caused no changes in gross behavior of rats, which shows that there were no harmful effects and moreover, all the rats remained healthy in all the experiment. Several workers while working on *Ganoderma lucidum* (Yang *et al.*, 2002) and *Hericium erinaceus* (Yang *et al.*, 2003) biopolymers have also reported similar results.

Hypolipidemic effect. The effects of CP, MP, and FP on plasma triglyceride and total cholesterol have been shown in Table 4. In the present investigation, the FP (24.3%) and MP (16.3%) group significantly decreased the level of plasma triglyceride, as compared to control group. Some recent studies (Davignon and Cohn, 1996) have indicated that decreased plasma triglyceride concentration was associated with a lower risk of coronary heart disease. The reduction in triglyceride level due to dietary fiber as observed in the present studies may be due to the direct interference of triglyceride absorption as well as increased excretion of triglyceride via fecal fat (Miettinen, 1987). Yang *et al.* (2002) while working with biopolymers of *Ganoderma lucidum*, have also reported that their polymers significantly decreased the concentration of triglyceride when administered orally in dietary induced hyperlipidemic rats.

Though administration of CP, MP, and FP in the dietary-induced hyperlipidemic rats lowered the total cholesterol concentration (14.2%, 6.7% and 28.5%) in plasma, respectively, however, FP group was found to be best among others. The hypolipidemic effect exerted by these biopolymers may be due to its high viscous nature (Ebihara and Schneeman, 1989), or/and might raise the secretion of pancreatic juice in rats (Ikegami *et al.*, 1990). As observed in the present studies, perhaps for this property, it could lower the triglyceride and total cholesterol adsorption by inhibiting the formation of micelles in the small intestine and by altering the physical characteristics of the intestinal mucosa of rats (Chen and Anderson, 1986).

Table 5 shows the effects of the *A. auricula-judae* CP, MP, and FP on the plasma HDL cholesterol, LDL cholesterol, and atherogenic index. As compared to the control group, the FP group reduced the LDL cholesterol levels

Table 3. Effect of biopolymers extracted from culture broth (CP), mycelia (MP), and fruiting bodies (FP) of *Auricularia auricula-judae* on growth parameters in dietary-induced hyperlipidemic rats for 4 weeks

Group[1)]	Body weight gain (g/day)	Food intake (g/day)	Food efficient ratio[2)]
Control	4.73 ± 0.15^{b}	20.04 ± 0.39^{NS}	0.24
CP	4.39 ± 0.15^{ab}	19.29 ± 0.34	0.23
MP	4.37 ± 0.15^{ab}	19.60 ± 0.63	0.22
FP	4.06 ± 0.10^{a}	19.16 ± 0.21	0.21

[1)] See Table 2.
[2)]Body weight gain/Food intake.
[NS]Not significant.
Each values are means ± S.E. (n = 9).
[a,b]Values with different superscript letters in the same column significantly different among the group at $p < 0.05$.

Table 4. Effect of biopolymers extracted from culture broth (CP), mycelia (MP), and fruiting bodies (FP) of *Auricularia auricula-judae* on plasma total cholesterol and triglyceride in dietary-induced hyperlipidemic rats for 4 weeks

Group[1)]	Triglyceride (mg/d*l*)	Total cholesterol (mg/d*l*)
Control	29.48 ± 0.59^{b}	103.69 ± 9.39^{b}
CP	28.45 ± 1.50^{b}	88.93 ± 5.40^{ab}
MP	24.69 ± 1.28^{a}	96.70 ± 5.68^{b}
FP	22.33 ± 1.23^{a}	74.10 ± 3.06^{a}

[1)]See Table 2.
Each values are means ± S.E. (n = 9).
[a,b]Values with different superscript letters in the same column significantly different among the group at $p < 0.05$.

Table 5. Effect of biopolymers extracted from culture broth (CP), mycelia (MP), and fruiting bodies (FP) of *Auricularia auricula-judae* on plasma HDL cholesterol, LDL cholesterol, and the level of atherogenic index in dietary-induced hyperlipidemic rats for 4 weeks

Group[1)]	HDL cholesterol (mg/d*l*)	LDL cholesterol[2)] (mg/d*l*)	Atherogenic index[3)]
Control	16.31 ± 1.00^{NS}	81.48 ± 9.70^{b}	5.54 ± 0.82^{b}
CP	17.37 ± 1.54	65.87 ± 5.06^{ab}	4.29 ± 0.48^{ab}
MP	16.47 ± 0.79	75.30 ± 5.83^{b}	4.96 ± 0.44^{b}
FP	17.78 ± 1.02	54.39 ± 4.08^{a}	3.19 ± 0.26^{a}

[1)]See Table 2.
[2)]Total cholesterol - HDL cholesterol - (Triglyceride/5).
[3)](Total cholesterol - HDL cholesterol)/HDL cholesterol.
[NS]Not significant.
Each values are means ± S.E. (n = 9).
[a,b]Values with different superscript letters in the same column significantly different among the group at $p < 0.05$.

and atherogenic index by as much as 36.4% and 40.9%, respectively. Similar results have also been recorded by several workers (Yang *et al.*, 2002). The plasma HDL cholesterol level in the FP group (9.0%) showed the highest among the groups.

A strong relationship has been documented between the plasma total cholesterol, triglyceride, LDL cholesterol and atherogenic index (Gurr and Harwood, 1991). A substantial reduction of total cholesterol, triglyceride, LDL cholesterol and atherogenic index in plasma observed in the present case may be due to a reduced production of cholesterol by the liver tissues (by inhibiting HMG-CoA reductase) and/or efficient removal of the LDL cholesterol by various tissues without subsequent renewal (Yang *et al.*, 2003). Plasma LDL values may be affected by modifications of very-low-density lipoprotein (VLDL) metabolism, including the rate of conversion of VLDL to LDL. Basically, nascent VLDL is converted to mature VLDL and to LDL through the loss of triglyceride by the action of lipoprotein lipase. Shen *et al.* (1998) suggested that the LDL cholesterol lowering effect of *Psyllium* is due to slow conversion of VLDL to LDL.

The plasma LDL may arise physiologically from the catabolism of VLDL (Bilheimer *et al.*, 1972; Sigurdsson *et al.*, 1975) which documents an inter-relationship of these two lipoprotein classes and hence of plasma cholesterol and triglyceride, suggesting a possible metabolic site for the lesion in combined hyperlipidemia.

The plasma HDL cholesterol, an indicator of anti-atherosclerosis, is generally involved in the transport of excess cholesterol to the liver for reprocessing. It has been reported by several workers (Kang and Song, 1997; Kim *et al.*, 1992) that some dietary fibers can elevate the plasma HDL cholesterol level. The increased HDL value in this investigation may be due to the lower conversion of HDL to LDL or by some other means. Kinnunen *et al.* (1983) have demonstrated that the triglyceride lowering effect in plasma may be due to the elevated lipoprotein lipase activity. Shen *et al.* (1998) and Dietschy *et al.* (1993) also reported that a reduced plasma LDL cholesterol level in dietary-induced hyperlipidemic animals in an improper lipid metabolism leading to an enhanced level of hepatic acetyl-CoA, which in turn participates in lipogenesis and is accumulated as lipid in the liver tissue. Present studies suggest that the risk of atherosclerosis may dependent on more the plasma LDL level than the total cholesterol level in the body system. The level of HDL cholesterol found to be inversely related to the risk of atherosclerosis (Ganong, 1987).

The present investigation demonstrated the potential of *A. auricular-judae* FP in reducing the level of cholesterol rich-LDL (which is quantitatively the most significant lipoprotein class in the control of serum cholesterol levels) and preserving the HDL at relatively high level. Such effects can help in reducing the risk of atherosclerosis. It is possible that the hypocholesterolemic effect of *A.auricula-judae* FP appeared to be due to the reduced cholesterol synthesis in the liver. Also, it can not be ruled out the possibility of combined effects (the inhibition of cholesterol absorption, and/or the inhibition of biosynthesis of LDL and acceleration of their fractional turnover) (Tokuda *et al.*, 1974; Vahouny *et al.*, 1987).

In the present study, the CP, MP and FP in *A. auricula-judae* were screened for their hypolipidemic activity. Among other experimental groups, the FP group was shown to have the potency to combat hyperlipidemia in dietary-induced hyperlipidemic rats. These results indicate the necessity to perform a dose-dependent experiment. Moreover, further comprehensive chemical and pharmacological investigations may help in elucidating the exact mechanism of hypolipidemic effects. Isolation of active principles of this mushroom may be helpful in preventive and therapeutic purposes to alleviate the hyperlipidemic status.

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