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Lipid-lowering Effect of Monascus Garlic Fermented Extract (MGFE) in Hyperlipidemic Subjects

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ABSTRACT

Monascus Garlic Fermented Extract (MGFE) is a unique material produced from garlic fermented using *Monascus pilosus*, which contains characteristic compounds such as dimerumic acid and monacolin K. In this study, we examined the effect of MGFE on hyperlipidemic subjects. Fifteen subjects aged 33–59 years (11 men and 4 women) participated. All the subjects had either hypercholesterolemia (≥ 220 mg/dl) or hyper-low-density lipoprotein cholesterolemia (≥ 140 mg/dl), but only 4 of the 15 (27%) were hypertriglycemic (≥ 150 mg/dl). All subjects received two capsules of MGFE (225 mg/capsule) after breakfast and dinner for 4 weeks. After an overnight fast, blood was taken 0, 2 and 4 weeks after the start of MGFE intake, and 2 weeks after MGFE withdrawal. MGFE significantly reduced serum total cholesterol (TC) and low-density lipoprotein cholesterol levels 2 and 4 weeks after the start of MGFE intake as compared with the baseline. Although the level of high-density lipoprotein cholesterol (HDL-C) was unaffected at any time, the atherogenic index calculated from the value of TC and HDL-C was significantly reduced 2 and 4 weeks after the start of MGFE intake. These effects of MGFE tended to disappear within 2 weeks after withdrawal. Triglyceride (TG) and lipid peroxide levels were not reduced dramatically, but TG levels in hypertriglycemic subjects tended to reduce as compared with the baseline value. No abnormal changes in blood biochemical parameters or adverse effects were observed in any of the subjects. Our present results indicate that MGFE attenuates hyperlipidemia, suggesting that MGFE is a potent agent for preventing arteriosclerotic diseases.

Key words: *Monascus pilosus, Garlic, Hyperlipidemia, Arteriosclerosis, Cholesterol*

The genus *Monascus* has been used for the preparation of fermented foods and beverages in Taiwan, China and Japan, and also used as a Chinese herbal medicine to improve blood circulation[17)]. Recently, metabolic products of fermentation with *Monascus* have also been utilized as a red pigment for food additives[37,39)] and as biological agents[8,24)].

Monascus Garlic Fermented Extract (MGFE) is a unique material produced from garlic (*Allium sativum* L.) fermented using *Monascus pilosus*. It is odorless and contains characteristic compounds such as dimerumic acid and monacolin K, both of which are produced by the fermentation, but are not contained in garlic itself. Dimerumic acid possesses antioxidative activities, as demonstrated by its radical scavenging activity[2,33)]. Monacolin K is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, which inhibits the formation of mevalonate from HMG-CoA[8,9)]. Consequently, it blocks cholesterol synthesis and increases transcription of the low-density lipoprotein (LDL) receptor gene. A large number of studies have demonstrated that HMG-CoA reductase inhibitors decrease serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels[10,11,16)]. Hyperlipidemia is a major risk factor for arteriosclerosis, and its prevention is thought to be very important because arteriosclerosis can lead to fatal cardiac and cerebral infarction

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[21,25,28,29]. In Japan, about 30% of deaths annually are due to coronary artery and cerebrovascular diseases.

We have previously demonstrated that MGFE attenuates hyperlipidemia, including hypercholesterolemia and hypertriglyceridemia, and atherosclerotic lesions in cholesterol-fed rabbits[32]. The present study was designed to evaluate the effectiveness of MGFE on hyperlipidemia in humans.

MATERIALS AND METHODS

Subjects

Subjects with a serum TC level of more than 220 mg/dl and/or with a serum LDL-C level of more than 140 mg/dl were recruited, excluding anyone who was taking any therapy that included a lipid-lowering agent. Before the beginning of the study, all subjects were fully informed in writing about the purpose, methods and expected benefits and adverse reactions. They were also informed of their right to refuse participation and withdraw from the study at any time. Written consent to participate was then obtained from the subjects.

Test supplement and methods

Four capsules of test supplement contained 900 mg of MGFE, which contained 2 mg of monacolin K.

All subjects received two capsules of test supplement (225 mg of MGFE per capsule) after breakfast and dinner for 4 weeks (900 mg of MGFE per day). Following an overnight fast, blood was taken from median cubital vein 0 (baseline), 2 and 4 weeks after the start of MGFE intake, and 2 weeks after MGFE withdrawal. Serum was obtained by centrifugation at 2000 × *g* for 15 min, and used for lipid and general biochemical examinations. TC, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) and lipid peroxide (LPO) were measured for lipid examination, and atherogenic index (AI) was calculated as: AI=(TC − HDL-C)/HDL-C[40]. General biochemical examination included total protein (TP), albumin, albumin/globulin ratio (A/G), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), blood urea nitrogen (BUN), creatinine and myoglobin. Measurement of lipids and general biochemical examinations were performed at Fukuyama Medical Laboratory Co., Ltd. (Hiroshima, Japan).

Statistical analysis

The results are expressed as means ± SD. Differences between the baseline (0 weeks) and each point were evaluated by paired *t* test. Statistical analyses were performed with STATISTICA™ (StatSoft JAPAN, Tokyo, Japan). Differences at $p < 0.05$ were considered to be significant.

RESULTS

The baseline characteristics of the study subjects are summarized in Table 1. Fifteen subjects (11 men and 4 women) participated. Their age range was 33 to 59 years, and the mean was 47 years. The range of body weight and body mass index (BMI) was 47 to 105 kg and 19.6 to 31.4 kg/m^2, and the mean was 65 kg and 23.2 kg/m^2, respectively. The range of baseline TC and LDL-C levels was 209 to 346 mg/dl and 109 to 231 mg/dl, respectively. Since the criterion for hyperlipidemia in Japan is ≥ 220 mg/dl TC and ≥ 140 mg/dl LDL-C, all of the subjects who participated were either hypercholesterolemic or hyper-LDL-cholesterolemic. On the other hand, the range of baseline TG was 76 to 263 mg/dl, and thus 4 (27%) of the 15 subjects were hypertriglycemic (≥ 150 mg/dl). None of the subjects were hypo-HDL-cholesterolemic (< 40 mg/dl).

The results of lipid examination are shown in Fig. 1. Serum TC and LDL-C levels were reduced significantly 2 and 4 weeks after the start of MGFE intake. The reductions in TC and LDL-C after 4 weeks of MGFE intake were 47 and 37

Table 1. Baseline characteristics in this study

	Men	Women	Total
N	11	4	15
Age (years)	43 ± 7 (33–52)	55 ± 3 (51–59)	47 ± 8 (33–59)
Height (m)	1.72 ± 0.07 (1.60–1.83)	1.52 ± 0.02 (1.50–1.55)	1.66 ± 0.11 (1.50–1.83)
Body weight (kg)	71 ± 13 (60–105)	48 ± 1 (47–49)	65 ± 15 (47–105)
BMI (kg/m^2)	24.0 ± 3.2 (20.0–31.4)	20.8 ± 1.0 (19.6–21.8)	23.2 ± 3.1 (19.6–31.4)
Serum lipid level (mg/dl)			
TC	246 ± 30 (211–312)	253 ± 63 (209–346)	248 ± 39 (209–346)
LDL-C	167 ± 34 (109–231)	165 ± 33 (140–212)	166 ± 32 (109–231)
HDL-C	67 ± 20 (46–109)	61 ± 13 (42–72)	65 ± 18 (42–109)
TG	109 ± 35 (76–196)	149 ± 82 (82–263)	120 ± 51 (76–263)

The data are expressed as mean ± SD, and the ranges are given in parenthesis. BMI was calculated as: BMI=Body weight/(Height)^2.

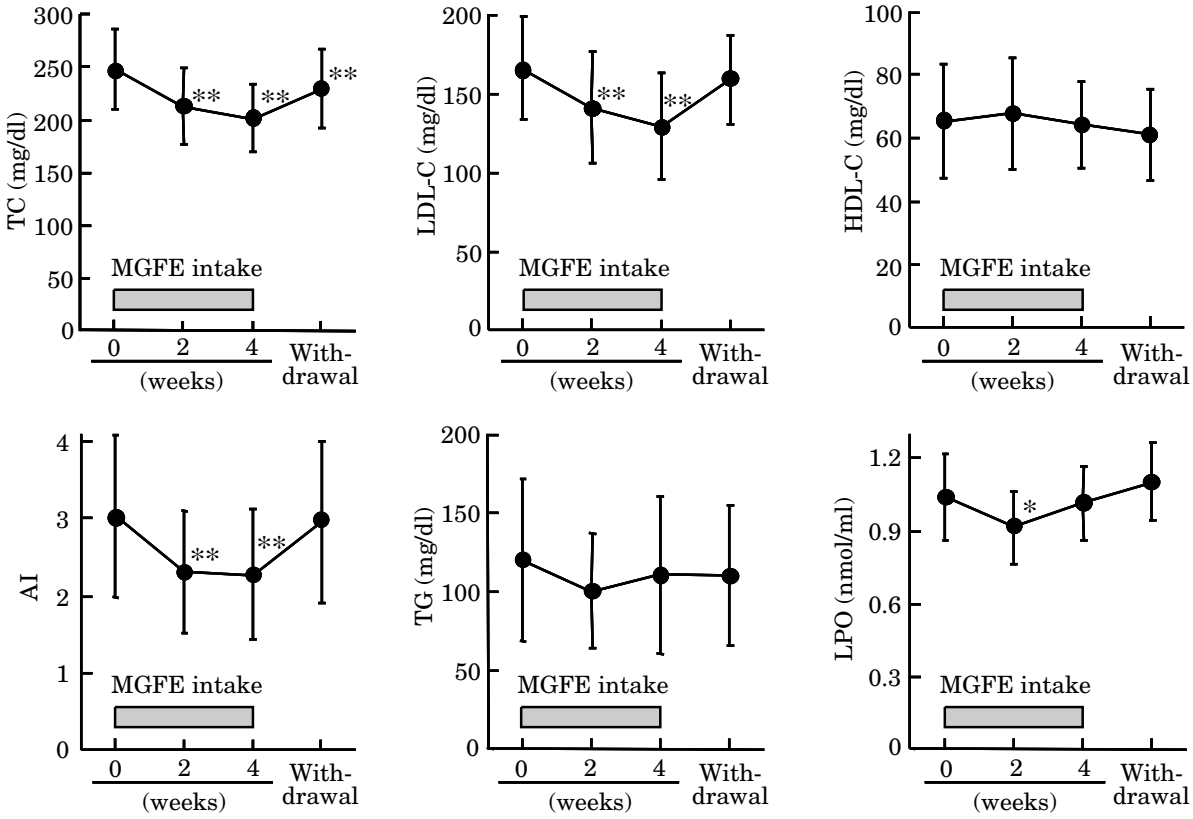

Fig. 1. Effect of MGFE intake on serum lipid levels.
MGFE (450 mg) was administered to subjects after breakfast and dinner (900 mg/day) for 4 weeks. Following an overnight fast, blood was taken 0, 2 and 4 weeks after the start of MGFE intake, and 2 weeks after MGFE withdrawal. TC, LDL-C, HDL-C, TG and LPO were measured, and AI was calculated as: AI=(TC − HDL-C)/HDL-C. The data are expressed as mean ± SD. *, **: Significant difference compared with the baseline level (0 week) ($p < 0.05$ and $p < 0.01$, respectively).

Table 2. Changes in serum TG in normal and hypertriglycemic subjects

Stratification by baseline TG	N	Baseline (actual value)	MGFE treatment (difference from the baseline)	
			2 weeks	4 weeks
< 150 mg/dl	11	94 ± 11	–9 ± 20	5 ± 52
≥ 150 mg/dl	4	191 ± 52	–49 ± 55	–49 ± 48

The data for 15 subjects were divided into hypertriglycemic (≥ 150 mg/dl) and normal (< 150 mg/dl) groups according to the baseline level, and analyzed for each group. The data are expressed as mean ± SD.

mg/dl on average, respectively. Although the HDL-C level was unaffected at any time by MGFE intake, AI calculated from the value of TC and HDL-C was significantly reduced 2 and 4 weeks after the start of MGFE intake. There was no difference between men and women in the TC- and LDL-C-lowering effects of MGFE (data not shown). These effects of MGFE tended to disappear within 2 weeks of withdrawal. TG showed a tendency to decrease as a result of MGFE intake, but not to a significant degree. Following stratification by the baseline TG level, the effect of MGFE on the serum TG level was analyzed again. As shown in Table 2, MGFE tended to decrease the serum TG level in hypertriglycemic subjects (≥ 150 mg/dl) at the baseline, and the reduction in TG after 4 weeks of MGFE intake was 49 mg/dl on average (n=4). On the other hand, the serum TG level in non-hypertriglycemic subjects (< 150 mg/dl) at the baseline was unchanged by MGFE intake. LPO showed a tendency to be decreased by MGFE intake, and the effect was significant after 2 weeks of MGFE intake.

General biochemical examination was conducted for clinical monitoring. MGFE decreased the serum creatinine level significantly in men 2 and 4 weeks after the start of MGFE intake, but the changes were all within normal limits. No significant changes were observed in other parameters (Table 3). Furthermore, no adverse effects were

Table 3. General biochemical parameters during MGFE intake

	Normal range	0 weeks	2 weeks	4 weeks
TP (g/dl)	6.5–8.2	7.39 ± 0.34	7.39 ± 0.43	7.33 ± 0.34
Albumin (g/dl)	3.7–5.2	4.62 ± 0.34	4.62 ± 0.30	4.53 ± 0.28
A/G	1.1–2.0	1.69 ± 0.30	1.69 ± 0.23	1.64 ± 0.24
AST (IU/liter)	8–40	20.9 ± 5.3	21.2 ± 4.0	19.9 ± 5.1
ALT (IU/liter)	4–45	25.1 ± 10.4	26.1 ± 12.2	26.8 ± 13.6
ALP (IU/liter)	100–340	237 ± 64	228 ± 59	236 ± 63
LDH (IU/liter)	120–240	180 ± 34	178 ± 29	172 ± 23
CPK (IU/liter)	Men: 45–280	143 ± 51	147 ± 59	167 ± 91
	Women: 30–180	80 ± 24	91 ± 35	99 ± 38
BUN (mg/dl)	8–22	14.2 ± 2.3	14.0 ± 3.2	13.9 ± 2.2
Creatinine (mg/dl)	Men: 0.60–1.10	0.96 ± 0.10	0.92 ± 0.11*	0.91 ± 0.11**
	Women: 0.45–0.80	0.65 ± 0.05	0.63 ± 0.04	0.64 ± 0.06
Myoglobin (ng/ml)	< 61	55 ± 12	51 ± 19	54 ± 14

MGFE (450 mg) was administered to subjects after breakfast and dinner for 4 weeks (900 mg/day). Following an overnight fast, blood was taken 0, 2 and 4 weeks after the start of MGFE intake, and general biochemical examination was performed. The data are expressed as mean ± SD. *, **: Significant difference compared with the baseline level (0 week) ($p < 0.05$ and $p < 0.01$, respectively).

observed in any of the subjects.

DISCUSSION

We have previously demonstrated that MGFE attenuates hyperlipidemia and decreases atherosclerotic lesions in cholesterol-fed rabbits[32]. The present study was designed to evaluate the effectiveness of MGFE for hyperlipidemia in humans.

MGFE intake in hyperlipidemic subjects for 4 weeks reduced serum TC and LDL-C levels and AI significantly. It is thought that monacolin K, a HMG-CoA reductase inhibitor, present in MGFE contributes to the cholesterol-lowering effect. Monacolin K is thought to inhibit the formation of mevalonate from HMG-CoA, block cholesterol synthesis, and upregulate transcription of the LDL receptor gene[8,10]. Many clinical studies have shown that monacolin K (Lovastatin) at a dosage of 10 to 80 mg/day decreases the serum level of TC and LDL-C[7,13-15,18,34-36]. The dosage of MGFE (900 mg/day) used in this study was equivalent to only 2 mg/day monacolin K. Although this dosage was small in comparison with that used in many of the clinical studies mentioned above, it was enough to decrease the serum TC and LDL-C levels in individuals with mild hypercholesterolemia and hyper-LDL-cholesterolemia. Since all clinical reports of monacolin K were performed in America, population differences, body weight, BMI and drug sensitivity of subjects between studies may affect the serum cholesterol-lowering effect. Indeed, the mean of body weight and BMI in this study was 65 kg and 23.2 kg/m^2, and both values were smaller than those of previous studies performed in America[7,18,35,36]. In addition, whether or not subjects were hyperlipidemic, accompanied by cardiovascular disease and/or familial hypercholesterolemia, is thought to be an important factor in assessing the degree of its cholesterol-lowering effect. Finally, this cholesterol-lowering effect of MGFE may involve other constituents produced by garlic fermentation besides monacolin K. We have demonstrated that MGFE contains dimerumic acid, riboflavin and thymine besides monacolin K, all of which are newly produced by garlic fermentation. But these compounds are insufficient to explain the cholesterol-lowering effect of MGFE. Further studies will be warranted to elucidate its efficacy.

Since hypercholesterolemia and hyper-LDL-cholesterolemia are major risk factors for arteriosclerosis[21,25,28,29], it is thought that MGFE would be useful for preventing arteriosclerotic diseases such as cardiac angina and cardiac and cerebral infarction. In addition to hypercholesterolemia and hyper-LDL-cholesterolemia, hypertriglycemia also is thought to be a risk factor for arteriosclerosis[3,4,19,20]. This study showed that MGFE did not decrease the serum TG level significantly. Since only 4 (27%) of the 15 subjects were hypertriglycemic (≥ 150 mg/dl) at the baseline, we thought it would be difficult to detect any triglyceride-lowering effect of MGFE. Analysis following stratification by baseline TG showed that MGFE decreased the serum TG level in hypertriglycemic subjects, but had no equivalent effect in non-hypertriglycemic subjects. These data suggest that MGFE intake in hypertriglycemic subjects may decrease the level of serum TG. We have ascertained that MGFE suppresses apolipoprotein B secretion *in vitro* using HepG2 cells (unpublished data). Therefore, suppression of the secretion of very low density lipoprotein through a decrease in apolipoprotein B may be one of the mechanisms underlying the TG-lowering effect of MGFE. Further studies will be required to confirm the effectiveness of MGFE against hypertriglycemia.

Recently, persons who possess multiple risk factors for the development of cardiovascular disease (i.e., abdominal obesity, diabetes, insulin resistance, dyslipidemia, and/or hypertension), a pathologic condition known as metabolic syndrome, are increasing worldwide[12,23,26]. Therefore, it is considered that countermeasures against hyperlipidemia will become increasingly important in the future.

In the arteries of hypercholesterolemic patients, vascular superoxide production and oxidative stress are increased[27]. Oxidation of LDL is considered to be an important step in the development of atherosclerosis. Oxidized LDL (ox-LDL) is readily taken up by the scavenger receptor of macrophages, and converts them to foam cells, which are components of atherosclerotic plaque[30,31]. Furthermore, ox-LDL plays other roles in atherogenesis; for example, it is injurious to the vascular endothelium and stimulates smooth muscle cell proliferation and, hence, fibrosis[5,30]. Antioxidants such as vitamin E and probucol protect LDL from oxidation, and prevent the development of atherosclerosis[6,22,38]. Since MGFE contains dimerumic acid, an antioxidant, the possibility has been suggested that, like vitamin E and probucol, MGFE may suppress ox-LDL formation. Indeed, LDL in rabbits treated orally with MGFE for 17 weeks showed a tendency to be resistant to LDL oxidation[32]. Anderson et al have demonstrated that combination therapy with a cholesterol-lowering agent and an antioxidant improves not only serum TC and LDL-C levels, but also the endothelium-dependent vasodilative response to acetylcholine[1]. Therefore, it is thought that MGFE, which contains both an antioxidant component and a lipid-lowering component, would be highly effective for the prevention of arteriosclerotic disease.

With regard to the safety of MGFE, no abnormal changes in blood biochemical parameters or adverse effects were observed in any of the subjects. Though the level of serum creatinine in men was significantly reduced 2 and 4 weeks after the start of MGFE intake, the changes were not thought to be a clinically important problem, because they were all within normal limits. A variation of lifestyle such as meal and exercise during the period of this study may be the cause of a slight decrease in serum creatinine. These findings suggested that MGFE is safe and useful for preventing hyperlipidemia.

In conclusion, we have demonstrated that MGFE attenuates hyperlipidemia, especially hypercholesterolemia and hyper-LDL-cholesterolemia, which are major risk factors for arteriosclerosis. These data suggest that MGFE can act as a potent preventive agent against arteriosclerotic disease.

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