# Effects of *Antrodia Camphorata* Mycelia Extract Containing Antroquinonol on Lowering Low-Density Lipoprotein Cholesterol: A Randomized Double-Blind Study

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**Abstract:** *Objective*: *Antrodia camphorata* is a type of true fungus that grows only on *Cinnamomum camphora* trees, also known as *Cinnamomum kanehirae* ("kashi") in Taiwan. Antroquinonol is a characteristic component of *A. camphorata* mycelia extract and was previously shown to exhibit antitumor action and lower blood cholesterol (total cholesterol and low-density lipoprotein [LDL] cholesterol) in cellular and animal models. So, This study examined the ability of *A. camphorata* mycelia extract to reduce LDL cholesterol in humans.

*Methods*: We conducted a randomized double-blind trial in 26 subjects with either borderline LDL cholesterol (120–139 mg/dL; n = 11) or mildly elevated LDL cholesterol (140–159 mg/dL; n = 15). Participants ingested tablets containing either 25 mg of *A. camphorata* mycelia extract (antroquinonol: 0.68 mg; n = 14) or a placebo (n = 12) for 12 weeks.

*Results*: The test group showed a significant reduction in LDL cholesterol when compared with the placebo group after 12 weeks of tablet ingestion ($p < 0.05$), demonstrating the effects of *A. camphorata* mycelia extract on LDL cholesterol. *A. camphorata* mycelia extract also tended to reduce total cholesterol when compared with the placebo ($p < 0.10$). The borderline LDL cholesterol and mildly elevated LDL cholesterol subgroups showed a significant reduction in LDL cholesterol in subjects who ingested *A. camphorata* mycelia extract compared with those who ingested the placebo, again demonstrating the LDL cholesterol-lowering effect of the extract.

*Conclusion*: *A. camphorata* mycelia extract lowers LDL cholesterol in individuals with somewhat high LDL cholesterol levels.

This clinical trial was registered with the University Hospital Medical Information Network (UMIN no. # 000019670).

**Keywords:** *Antrodia camphorate*, Antroquinonol, LDL-cholesterol, LDL receptor genes, randomized placebo-controlled double-blind study.

## INTRODUCTION

Dyslipidemia is a risk factor for coronary artery diseases, such as arteriosclerosis. Arteriosclerosis can result from low-density lipoprotein (LDL) entering the arterial wall below the vascular endothelial cells. This process is accompanied by the generation of oxidized LDL, formation of foam cells, proliferation of smooth muscle cells, and vascular wall calcification, ultimately leading to the formation of atherosclerotic plaques that can interrupt blood flow [1]. Many epidemiological studies have reported that increases in total serum cholesterol and LDL cholesterol levels greatly influence the onset of arteriosclerosis [2-5]. Attempts are being made to improve cholesterol levels via dietary changes and nutritional guidance [6, 7]. Many components in foods, such as plant sterols [8, 9] and pine bark extract [10], exhibit LDL cholesterol-lowering effects. In February 2015, a scientific report for the general public by the Dietary Guidelines Advisory Committee of the United States Department of Agriculture [11], indicated that conventional restrictions on cholesterol ingestion should be eliminated because there was no clear evidence linking the ingestion of cholesterol in food to blood cholesterol levels. Similarly, the Japanese 2015 Dietary Reference Intake (DRI) levels do not restrict cholesterol intake because there is insufficient evidence of a correlation between the dietary intake of cholesterol and blood cholesterol levels in healthy

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individuals. However, the Japan Atherosclerosis Society continues to issue alerts regarding the intake of cholesterol by individuals with high LDL cholesterol levels [12]. Lowering LDL cholesterol is thought to be effective at reducing the risks for conditions such as arteriosclerosis.

*Antrodia camphorata* is a type of true fungus that grows only on *Cinnamomum camphora* trees, also known as *Cinnamomum kanehirae* ("kashi") in Taiwan [13]. This fungus has been widely used in ancient folk medicine as well as in foods and medicinal products. In recent years, because *C. kanehirae* trees in Taiwan have approached extinction, they have been widely replaced by *A. camphorata* mycelia in foods through advances in cultivation techniques. *A. camphorata* mycelium was added to Japan's "Non-medicinal Product List" in 2015 following reform of the Food and Drug Classification List after safety of its ingestion was proven. Indeed, *A. camphorata* mycelium is now used as a health food. The mycelium contains various nutrients and bioactive components, such as polysaccharides and triterpenoids. Golden Biotech (New Taipei City, Taiwan) has used its own original solid-state culture technology to cultivate high-quality *A. camphorata* mycelia. This has allowed the successful induction and extraction of low molecular weight antroquinonol (M.W. 390) (Figure **1**), which is not present in normal *A. camphorata* mycelia. Antroquinonol has been confirmed to exhibit antitumor action and preventive effects against Alzheimer disease, improve systemic lupus erythematosus (an autoimmune disease), protect the liver, and reduce fatigue in cellular and animal models [14-19].

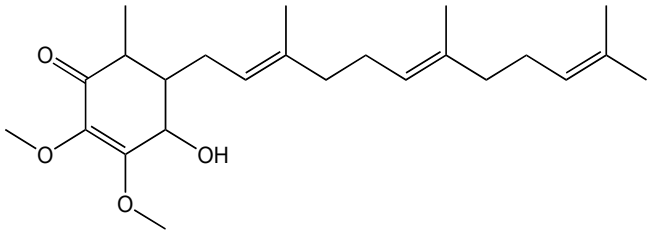


**Figure 1:** Structure of antroquinonol.

Although animal and cellular experiments showed that *A. camphorata* mycelia extract exhibits various physiological actions, little evidence is available regarding its effect on humans. Therefore, we conducted a randomized double-blind study to assess the ability of *A. camphorata* mycelia extract to lower LDL cholesterol and total cholesterol in individuals with somewhat high levels of LDL cholesterol.

## MATERIAL AND METHODS

### Antrodia Camphorata Extract

*A. camphorata* mycelia extract is a supercritical extraction of *A. camphorata* mycelia powder that contains antroquinonol.

### Test Material

The test material was a tablet containing 25 mg of *A. camphorata* mycelia extract (antroquinonol: 0.68 mg). Subjects ingested one tablet per day. The placebo was a tablet that did not contain *A. camphorata* mycelia extract (Table **1**). The two types of tablets could not be distinguished by appearance or taste. Neither the test material nor the placebo contained any other ingredient that affected blood lipid or blood cholesterol levels. Antroquinonol was isolated and characterized as described in a previous study [13].

**Table 1: Composition of the Test and Placebo Tablets**

| Components | Test | Placebo |
|---|---|---|
| *Antrodia camphorata* extract | 25 mg | 0.0 mg |
| Antroquinonol | 0.68 mg | 0.00 mg |
| Energy | 0.0745 kcal | 0.0886 kcal |
| Water | 1.000m g | 0.175mg |
| Protein | 0.075mg | 0.05mg |
| Fat | 2.88mg | 0.80mg |
| Carbohydrates | 20.55m g | 22.63 mg |
| Sodium | 0.002 mg | 0.006 mg |
| Equivalent amount of table salt | 0.0058mg | 0.0156 mg |

### Cell Lines and Cell Culture

Human liver cancer cell line HepG2 cells were obtained from the American Type Culture Collection (Rockville, MD, USA). The cells were cultured at 37°C in 5% $CO_2$ in Minimum Essential Medium culture medium supplemented with 10% fetal bovine serum and 100 U/ml streptomycin and penicillin. For treatment, cells were seeded in six-well plates at $6.25 \times 10^5$ cells/well. On the following day, the medium was changed to a serum-free medium and cells were serum-starved for 24 h. Antroquinonol was dissolved in dimethyl sulfoxide and diluted to the required concentration in serum-free medium. Cultures were then treated with diluted antroquinonol as indicated.

### RNA Extraction and Reverse Transcription PCR

After treatment, cells were washed with cold phosphate-buffered saline and total RNA was extracted using the RNeasy mini kit (Qiagen, Hilden, Germany). Total RNA (1 μg) was reverse-transcribed into cDNA using SuperScript® III Reverse Transcriptase (Invitrogen, Illkirch, France) and oligo(dT)12–18 primers. Polymerase chain reaction (PCR) analysis was performed using LDLR-specific primers (LDLRF: 5' CTTTCAACACACAACAGCAGA 3' and LDLRR: 5' TGACAGGGCAAAGGCTAAC 3') and GAPDH-specific primers (GAPDHF: 5' GGTATCGTGGAAGGACTCAT 3' and GAPDHR: 5' CCTTGCCCACAGCCTTG 3'). The correct size of the amplified region for each primer was verified using agarose gel electrophoresis. Data were analyzed with PCR efficiency correction using Light Cycler 480 Relative Quantification software v1.01 (Roche) based on relative standard curves corresponding to the PCR amplification efficiencies of *LDLR* and *GAPDH* genes.

### Subjects

Subjects were Japanese men and women with borderline or mildly elevated levels of LDL cholesterol (120-159 mg/dL) [20]. The inclusion criterion was a borderline (120-139 mg/dL) or mildly elevated (140-159 mg/dL) LDL cholesterol level based on the notes of caution for applications of Japanese Foods for Specified Health Uses [21]. Exclusion criteria were as follows: 1) receiving medication; 2) heart or liver dysfunction; 3) a borderline total cholesterol level of 200–239 mg/dL, LDL cholesterol level >160 mg/dL, and high-density lipoprotein (HDL) cholesterol level ≤40 mg/dL; 4) aged younger than 20 years; and 5) participation deemed inappropriate by the principal investigator for medical reasons.

### Ethics Review Board

The present study was conducted in accordance with the guidelines of the Declaration of Helsinki, the Ethical Guidelines for Biomedical Research Involving Human Subjects, and notes of caution for applications of Japanese Foods for Specified Health Uses. Prior to commencement, the study was reviewed and approved by the Oriental Ueno Medical Center Ethical Review Board as conforming to the principles of the Declaration of Helsinki [22]. The study purpose and investigation procedure were explained in detail to the subjects before the study commenced, and each subject completed a consent form before participation. This clinical trial was registered with the University Hospital Medical Information Network (UMIN no. # 000019670).

### Test Procedure

The present study had a randomized placebo-controlled parallel design. The clinical study was conducted between November 2015 and March 2016. Screening tests were conducted for subjects who had fasted for at least 8 hours before arriving at our hospital (Figure **2**). The principal investigator selected 26 subjects who met the inclusion criteria and for whom the exclusion criteria did not apply. The selected subjects were randomly assigned to either the test group or the placebo group, and they ingested one tablet per day for 12 weeks. At 4, 8, and 12 weeks after starting ingestion, participants underwent blood tests and blood lipid measurements at our hospital. No dietary management was implemented during the test period.

### Randomization

Subjects were allocated into a test group or a placebo group using stratified randomization to prevent any bias in blood LDL cholesterol levels between groups. This allocation was conducted by someone not otherwise involved in the study, using a computer-generated table of random numbers. This person also verified the indistinguishability of the test product and placebo.

### Statistical Analysis

All data were expressed as the mean ± SE. Statistical analyses were conducted using SAS9.4 (SAS Institute) software. Student's t-tests were used for comparisons between groups. In addition to comparing the changes in lipid levels between the test and placebo groups, we also performed a stratified analysis of changes in LDL cholesterol for the subgroups of subjects with borderline and mildly elevated cholesterol levels. Differences in treatment values with a p-value $<0.05$ were considered statistically significant.

## RESULTS

Table **2** shows the background data for the study participants. There were 14 subjects in the test group and 12 subjects in the placebo group. Table **3** shows changes in blood lipids. Notably different trends for the change in total cholesterol after 8 and 12 weeks of ingestion were observed between the test and placebo groups, showing that total cholesterol tended to decrease in the test group ($p < 0.10$). The test group

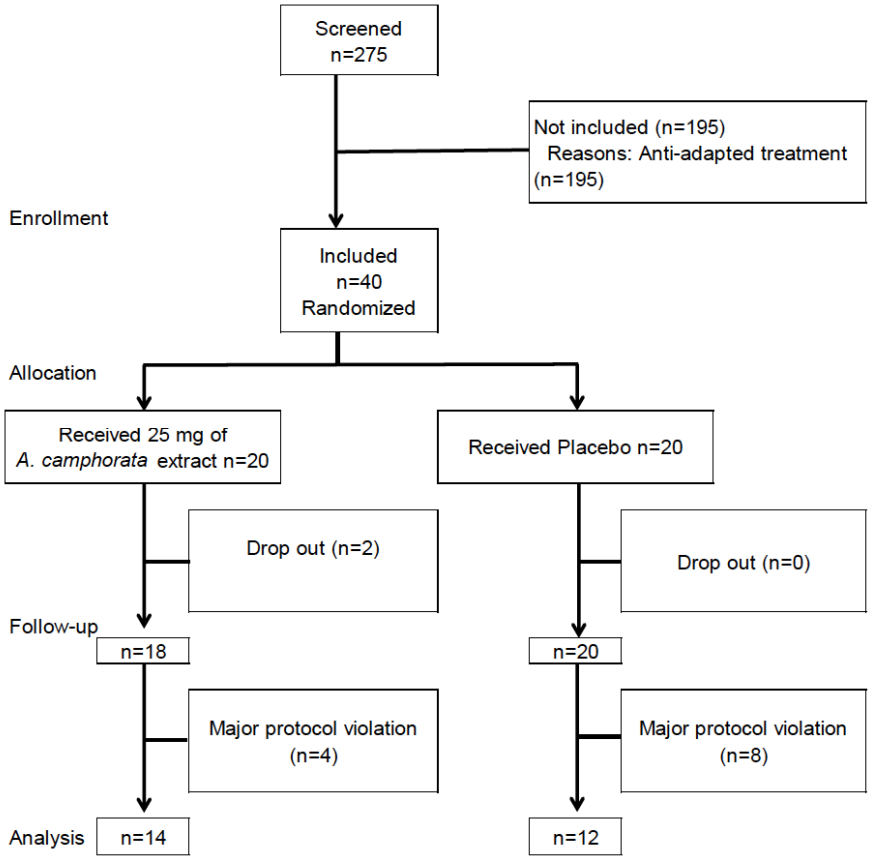


**Figure 2:** Flowchart of study participants.

**Table 2: Subject Characteristics**

| | Overall | | Borderline cholesterol (120-139 mg/dL) | | Midly elevated cholesterol (140-159 mg/dL) | |
|---|---|---|---|---|---|---|
| | **Test group** | **Placebo group** | **Test group** | **Placebo group** | **Test group** | **Placebo group** |
| n | 14 | 12 | 6 | 5 | 8 | 7 |
| Number of men and women (men/women) | 8/6 | 9/3 | 5/1 | 4/1 | 3/5 | 5/2 |
| Weight (kg) | 73.64 ± 8.05 | 74.28 ± 8.17 | 76.95 ± 5.22 | 73.10 ± 7.14 | 71.16 ± 9.19 | 75.13 ± 9.29 |
| BMI (kg/m$^2$) | 27.07 ± 1.32 | 26.93 ± 1.26 | 27.25 ± 1.57 | 26.76 ± 0.82 | 26.94 ± 1.21 | 27.04 ± 1.56 |
| Total cholesterol (mg/dL) | 217.8 ± 12.2 | 220.7 ± 13.5 | 210.0 ± 8.1 | 210.6 ± 12.3 | 228.8 ± 10.9 | 223.0 ± 9.9 |
| LDL cholesterol (mg/dL) | 142.0 ± 9.5 | 143.4 ± 11.1 | 133.7 ± 3.9 | 132.4 ± 4.3 | 148.3 ± 7.1 | 151.3 ± 6.4 |
| HDL cholesterol (mg/dL) | 62.6 ± 13.2 | 54.2 ± 14.8 | 59.8 ± 17.6 | 61.8 ± 16.1 | 64.6 ± 9.6 | 48.7 ± 12.0 |
| Triglycerides (mg/dL) | 113.4 ± 64.3 | 133.6 ± 45.0 | 120.5 ± 90.3 | 117.4 ± 34.1 | 108.0 ± 42.0 | 145.1 ± 50.6 |

showed a significant reduction in LDL cholesterol after 12 weeks of ingestion ($p < 0.05$) and a significant reduction in LDL cholesterol to HDL cholesterol (L/H) ratio ($p < 0.01$) after 8 and 12 weeks of ingestion compared with the placebo group. Interestingly, an increase in serum HDL-C levels was observed in the test group after 8 weeks of ingestion compared with the placebo group ($p < 0.05$). No significant differences

**Table 3: Changes in Blood Lipid Levels**

| Item | Unit | Group | n | Before ingestion | After 4 weeks of ingestion | After 8 weeks of ingestion | After 12 weeks of ingestion |
|---|---|---|---|---|---|---|---|
| Total cholesterol | mg/dL | Test group<br>Placebo group | 14<br>12 | 220.7 ± 3.6<br>217.8 ± 3.5 | 218.7 ± 4.8<br>227.6 ± 3.9M | 217.2 ± 4.7<br>225.8 ± 3.7† | 215.8 ± 3.3<br>225.0 ± 4.5 |
| LDL cholesterol (LDL-C) | mg/dL | Test group<br>Placebo group | 14<br>12 | 142.0 ± 2.5<br>143.4 ± 3.2 | 137.4 ± 3.8<br>147.3 ± 5.0 | 136.6 ± 4.9<br>151.4 ± 3.5† | 135.7 ± 2.6 *#<br>148.6 ± 5.0 |
| HDL cholesterol (HDL-C) | mg/dL | Test group<br>Placebo group | 14<br>12 | 63.6 ± 3.5<br>54.2 ± 4.3 | 61.4 ± 4.2<br>54.8 ± 3.9 | 64.6 ± 3.1#<br>53.3 ± 3.5 | 63.2 ±2.7<br>55.2 ± 4.4 |
| L/H ratio (LDL-C/HDL-C) | - | Test group<br>Placebo group | 14<br>12 | 2.37 ± 0.52<br>2.69 ± 0.14 | 2.37 ± 0.24<br>2.87 ± 0.16 | 2.19 ± 0.14##<br>2.97 ± 0.20 | 2.19 ± 0.26#<br>2.91± 0.10 |
| Triglycerdes | mg/dL | Test group<br>Placebo group | 14<br>12 | 113.4 ± 17.2<br>133.6 ± 13.0 | 113.9 ± 23.2<br>146.1 ± 20.0 | 93.8 ± 14.9<br>123.7 ± 12.5 | 94.7 ± 12.0<br>116.7 ± 14.1 |
| Arteriosclerotic index | mg/dL | Test group<br>Placebo group | 14<br>12 | 2.66 ± 0.19<br>3.30 ± 0.33 | 2.76 ± 0.30<br>3.38 ± 0.30 | 2.45 ± 0.17##<br>3.40 ± 0.25 | 2.47 ± 0.12#<br>3.34 ± 0.31 |

Mean ± standard error. LDL, low-density lipoprotein; HDL, high-density lipoprotein.
*Results were compared with the level before ingestion using paired Student's t-test. † $p < 0.1$, *$p < 0.05$.
*Comparisons with the placebo group at each time point were performed using unpaired Student's t-test. # $p < 0.05$, ## $p < 0.01$.

were noted for changes in triglyceride levels. Arteriosclerotic indices differed significantly between groups after 8 and 12 weeks of ingestion ($p < 0.05$), indicating that ingestion of the test tablets lowered the risk for cardiovascular diseases.

Results of the stratified analysis of LDL cholesterol in subjects with borderline and mildly elevated cholesterol levels are shown in Table **4**, and changes in low-density lipoprotein cholesterol levels (ΔLDL-C) are shown in Figure **3**. In subjects who ingested test tablets, borderline cholesterol levels significantly decreased ($p < 0.05$) after 8 weeks of ingestion. Furthermore, changes in low-density lipoprotein cholesterol (ΔLDL-C) levels significantly decreased ($p < 0.05$) after 8 weeks of ingestion. In mildly elevated cholesterol subjects, a significant reduction ($p < 0.01$) was noted in LDL cholesterol after 4weeks and 12 weeks of ingestion. Furthermore, changes in low-density lipoprotein cholesterol (ΔLDL-C) levels significantly decreased ($p < 0.05$) after 12 weeks of ingestion. Among subjects who ingested the test tablet, a significantly larger reduction in serum LDL cholesterol levels was observed in subjects having mildly elevated cholesterol levels compared with subjects having borderline cholesterol levels.

Although a few adverse effects, such as abdominal distension and pain, were noted during the ingestion period, no causal relationship between these symptoms and the ingestion of test tablets was identified, and no effects of long-term ingestion was identified during the 12-week ingestion period. No significant changes in aspartate aminotransferase, alanine aminotransferase, or r-GT levels, which are indices for liver function, were identified in the test group during the 12-week ingestion period (data not shown). Thus, it can be inferred that daily ingestion of

**Table 4: Results of the Stratified Analysis of Changes in Low-Density Lipoprotein Cholesterol Levels**

| Item | Reference value | Unit | Group | n | Before ingestion | After 4 weeks of ingestion | After 8 weeks of ingestion | After 12 weeks of ingestion |
|---|---|---|---|---|---|---|---|---|
| Borderline cholesterol | 120.139 | mg/dL | Test group<br>Placebo | 6<br>5 | 133.7 ± 1.6<br>132.4 ± 1.9 | 131.5 ± 7.2<br>136.0 ± 7.9 | 120.0 ± 5.6†#<br>145.6 ± 5.7 | 132.0 ± 6.0<br>139.6 ± 8.6 |
| Mildly elevated cholesterol | 140-159 | mg/dL | Test group<br>Placebo | 8<br>7 | 148.3 ± 2.5<br>151.3 ± 2.4 | 141.8 ± 3.7#<br>155.4 ± 4.9 | 147.0 ± 4.1<br>155.6 ± 4.0 | 138.0 2.2 *##<br>155.0 ± 5.1 |

Mean ± standard error.
*Results were compared with the level before ingestion using paired Student's t-test. † $p < 0.1$, *$p < 0.05$.
*Comparisons with the placebo group at each time point were performed using unpaired Student's t-test. # $p < 0.05$, ## $p < 0.01$.

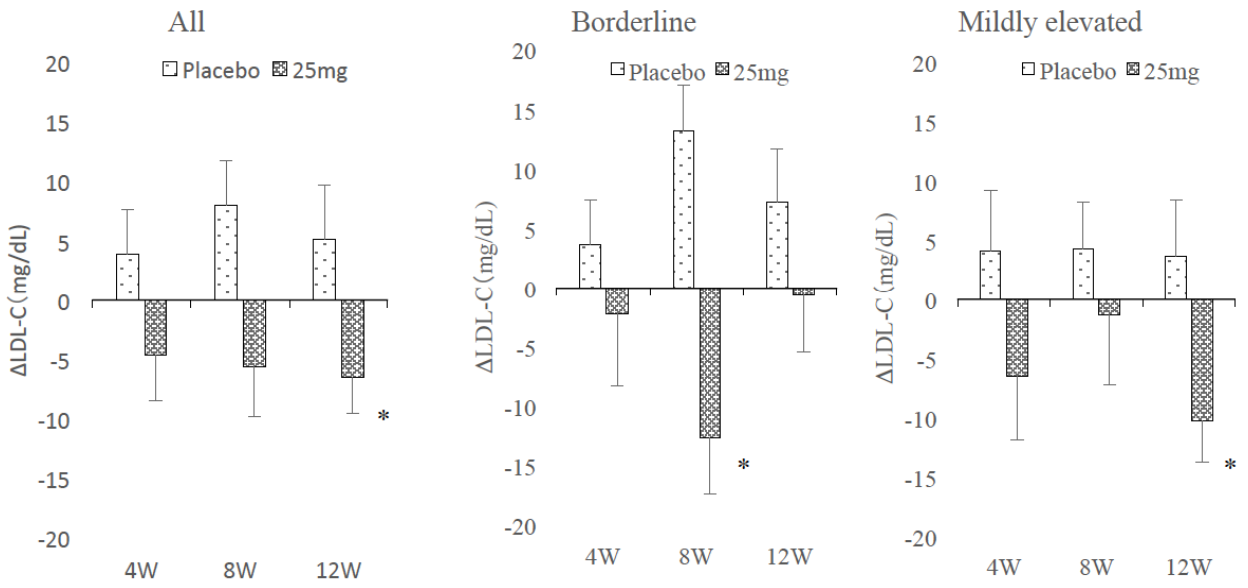


**Figure 3:** Changes in low-density lipoprotein cholesterol (ΔLDL-C). The graphs compare the groups taking the placebo and 25 mg of *A. camphorata* mycelia extract for 4, 8, and 12 weeks (W) for all subjects (n = 26), borderline cholesterol subjects (n = 11), and mildly elevated cholesterol subjects (n = 15). * $p < 0.05$ compared with the placebo.

*A. camphorata* mycelia extract over 12 weeks had no adverse effects on liver function.

## DISCUSSION

The findings of our present study indicate that ingestion of *A. camphorata* mycelia extract containing antroquinonol lowered LDL cholesterol in healthy subjects with somewhat high plasma LDL cholesterol concentrations. These effects were noted in subjects having both borderline and mildly elevated LDL cholesterol levels, indicating that *A. camphorata* mycelia extract is widely effective in individuals with somewhat high LDL cholesterol levels. In the body, more than half of LDL cholesterol catabolism takes place via a receptor-mediated pathway. An apolipoprotein, ApoB-100, which is virtually the only protein in the LDL particle, binds with LDL receptors in cells before the LDL particle is taken up into the cell and metabolized. *A. camphorata* mycelia extract containing antroquinonol has been shown in a cellular experiment to increase the expression of LDL receptor genes (Figure **4**), suggesting that the activation of the LDL receptor results in LDL cholesterol-lowering effects. A recent study indicated that a crude extract of *A. camphorata* reduced total lipids in the liver and plasma [23]. From this, it was inferred that a crude extract of *A. camphorata* containing antroquinonol might have high potency for the management of plasma lipid disorders. Our present study showed that ingesting *A. camphorata* mycelia extract containing antroquinonol also reduced LDL cholesterol levels in plasma. Notably, the ingestion of *A. camphorata* mycelia extract containing antroquinonol significantly reduced LDL cholesterol levels; thus, it appears that antroquinonol is at least one of the functional components of the *A. camphorata* mycelia extract responsible for its LDL cholesterol-lowering effects.

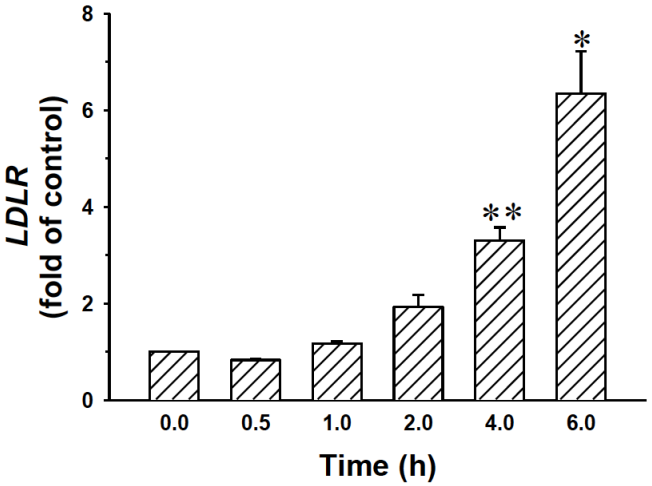


**Figure 4:** Effect of antroquinonol on *LDLR* gene expression in HepG2 cells. Real-time quantification of the *LDLR* mRNA level in HepG2 cells treated with 20 μM antroquinonol for 0, 0.5, 1, 2, 4, and 6 h. Data are presented as the mean ± SEM of at least three independent experiments. * $p < 0.05$, ** $p < 0.01$ compared with the respective basal.

## CONCLUSIONS

The present study investigated the LDL cholesterol-lowering effects of *A. camphorata* mycelia extract containing antroquinonol in subjects with somewhat

borderline and mildly elevated LDL cholesterol levels. Our findings indicate that taking the extract over several weeks significantly lowered LDL cholesterol levels. A stratified analysis also showed that LDL cholesterol was reduced in subjects with both borderline cholesterol and mildly elevated cholesterol levels. These results suggest that ingestion of *A. camphorata* mycelia extract containing antroquinonol is effective for improving LDL cholesterol levels in individuals with somewhat borderline and mildly elevated LDL cholesterol levels.

## CONFLICT OF INTEREST

This study was funded by Golden Biotechnology Corp. Miles Chih-Ming Chena, Pei-Ni Chena, Howard Hao-Yu Chenga, Wayne Ching-Cheng Weia are employees of Golden Biotechnology Corp.

## ABBREVIATIONS

LDL = low-density lipoprotein

HDL = high-density lipoprotein

LDLR = low-density lipoprotein receptor

UMIN = University Hospital Medical Information Network

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