Improvement of liver function by the administration of oyster extract as a dietary supplement to habitual alcohol drinkers: A pilot study

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Abstract. Alcoholic liver disease (ALD) is characterized by elevated serum γ-glutamyltransferase (GGT) activity with hepatic steatosis, hepatitis or occasionally fibrosis that may progress to cirrhosis. The potential therapeutic role of oyster extract (OE) or OE-containing dietary supplements (OE supplement) in ALD has seldom been evaluated. In the present study, 84 adults who had an alcohol-drinking habit and marginally high serum GGT levels were enrolled in a randomized, double-blind, placebo-controlled feeding trial to study the effect on alcohol-impaired liver function as reflected by an increased serum level of GGT, as well as the safety, of an OE supplement. The subjects were randomized to receive either an OE supplement (OE group) or placebo (placebo group). There were 42 subjects (31 males and 11 females) in each group, and all the enrolled subjects entered the study. Four individuals (5%) dropped out for reasons unassociated with the study and 6 other subjects were excluded from the efficacy analysis because they did not maintain the required frequency of alcohol intake. As a result, 38 subjects in the placebo group and 36 in the OE group underwent efficacy assessment. Assays of GGT and other liver enzymes were performed at baseline (week 0) and at weeks 4, 8 and 12 of the intervention period. The mean serum levels of GGT in the placebo group gradually increased, while those in the OE group tended to decrease, although no significant within-group differences were observed for either group. A significant between-group difference in the change of mean GGT from baseline was, however, found at week 12 (P=0.049). No OE supplement-associated untoward side-effects nor any abnormal changes in routine laboratory tests and anthropometric parameters were observed throughout the 12-week intervention. An OE supplement shows promise in reducing risk factors associated with ALD in adults with an alcohol intake habit.

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Introduction

Alcohol consumption is customary in the majority of cultures and alcohol abuse is common worldwide. The burden of excessive alcohol consumption-associated disease and mortality remains significant in numerous countries including Asian countries, such as China, Korea and Japan. The World Health Organization reported that, globally, alcohol is responsible for ~4% of all mortality and alcoholic liver disease (ALD) accounts for one-quarter of all alcohol-attributable fatalities (1). In China, alcohol abuse has been considered the second leading cause of liver disease (2). A similar trend of alcohol consumption-associated burden of disease, in particular ALD, has also been seen in Korea (3,4), as well as in Japan (5,6).

The most prevalent type of ALD is alcoholic fatty liver (or hepatic steatosis) and a significant subset of the individuals with hepatic steatosis progress to severe alcoholic hepatitis, of which the 6-month mortality rate is ≤40% (7). Severe alcoholic hepatitis also places an enormous burden on stretched healthcare resources (8,9). Unfortunately, however, there is no established therapy for ALD, and the treatment has been limited to supportive management and nutritional supplementation without clear improvements in outcome (10,11). There is, therefore, a rationale for preventing habitual alcohol drinkers from developing steatosis, an initially occurring reversible-type of liver injury.

Taurine (2-aminoethanesulfonic acid), a non-metabolizable sulfur-containing β-amino acid, is a major free intracellular amino acid present in numerous tissues of humans and animals (12). Taurine has been shown to have beneficial

effects on liver injury in various animal models. For example, taurine supplementation prevents hepatic steatosis and other alcohol-induced liver diseases in rats (13-15) and the development of steatosis in hamsters fed with high-fat/cholesterol diets (16). Despite convincing evidence in animal models, studies examining the metabolic response to supplementation with taurine in the context of alcoholic liver injury or dysfunction in humans are lacking, particularly in Japanese and other Asian nations who have a high proportion of poor alcohol metabolizers due to a genetic deficiency in the enzyme aldehyde dehydrogenase (17,18).

Oyster extract (OE) in a powder form is a nutraceutical that is produced from a species of oyster (*Crassostrea gigas*) by a biochemical preparation process. In Japan, several dietary supplements containing powdered OE are commercially available and particularly popular among habitual alcohol drinkers who are at a high risk of ALD. The objective of the present human study was to assess the effects of 12 weeks of consumption of OE-containing supplements (OE supplement) on the serum levels of γ-glutamyltransferase (GGT) in Japanese adults with an alcohol-drinking habit. Serum GGT levels were selected as the major outcome measure as the enzyme is an established biomarker of liver function and chronically heavy alcohol intake (19-21).

Subjects and methods

Study design and ethics. A randomized, double-blind, placebo-controlled study was designed to assess the efficacy and safety of the OE supplement for improving the alcohol-impaired liver function in enrolled subjects when compared with placebo. The study was performed from May 2013 through September 2013 at the Medical Corporation Kenshokai, Fukushima Healthcare Center (Osaka, Japan). The study protocol was approved by the Ethics Committee of the Fukushima Healthcare Center (approval date, 10 May 2013) and was in accordance with the principles of the Helsinki Declaration of 1995 (as revised in October 2008) and the Ethical Guidelines for Epidemiological Research (enacted in 2004 and revised in 2008 by the Japanese Government). Written informed consent was obtained from all study subjects prior to their enrollment in the study. To ensure privacy, all records were identified with an anonymous subject identification number.

Subjects and eligibility. A total of 84 Japanese adults, aged 20-65 years, consisting of males and females at a ratio of ~7 to 3 who had an alcohol drinking habit (5-7 times per week), a GGT level between 50 and 150 IU/l and a body mass index (BMI) between 18 and 30 kg/m^2, were voluntarily recruited and included in this study. Individuals were excluded if they were: i) Currently taking medications, health foods and/or foods for specified health uses that may alter alcohol metabolism or liver enzyme activities; ii) habitually consuming OE; iii) positive for hepatitis virus tests (e.g., hepatitis B surface antigen and anti-hepatitis C virus antibody); iv) at risk of developing a study-associated allergic reaction, having a history of serious disease that required regular medication; v) with abnormal values of anthropometric, physiological or laboratory test parameters appreciably deviated from the normal range; vi) participating in any other clinical trial at the start time of the present study; vii) pregnant or breastfeeding; and viii) with the presence of any clinically significant medical condition that was judged by the medical investigator to preclude the inclusion of the participant in the study.

Dietary intervention and subject assignment. The OE supplement used in this study was a commercially available product manufactured by Bizen Chemical Co. Ltd. (Okayama, Japan) in the form of a 386 mg tablet containing 333 mg powdered OE, whose major constituents are glycogen (>50% w/w) and taurine (>5% w/w). The tablet also contained a 53 mg vehicle mixture of yeast cell wall, sucrose esters of fatty acids, tricalcium phosphate, maize protein, shellac, glycerin, titanium dioxide and carnauba wax. In the placebo tablet, OE was replaced by maltitol, dextrins and microcrystalline cellulose, in a total amount of 386 mg, and the contents were colored to make them similar in appearance to the contents of the OE supplement tablet.

Throughout the 12-week treatment period, each subject was required to keep a study diary of their allocated tablet intake, alcohol consumption, dietary composition, physical activity as measured by a passometer, all medications or therapies received, and any adverse events experienced. The subjects were also instructed to maintain their usual habits of alcohol drinking, food and beverage intake and current exercise program and to avoid the intake of health foods that may alter liver function.

The study intervention began ~1 week following the screening of eligible subjects. Male and female subjects were separately and sequentially assigned one of the two types of the masked study tablet (OE supplement or placebo) based on random number tables and were randomized (1:1) to the OE supplement (OE group) and placebo (placebo group). The subjects were required to consume three tablets of either OE supplement (1,000 mg as OE and >50 mg as taurine) or placebo products daily prior to the evening meal with the aid of a cup of water over the 12-week intervention period. Consumption of <80% of the prescribed course of the allocated product was considered as non-compliance and non-compliant subjects were excluded from the efficacy assessment.

To assess efficacy and safety, medical inspections, measurements of serum liver enzyme levels and anthropometric and hemodynamic parameters, as well as other laboratory tests, were performed prior to the start of intervention (week 0) and at weeks 4, 8 and 12.

Laboratory tests for serum analysis and urinalysis. A commercial laboratory test company (Mitsubishi Chemical Medience Corporation, Osaka, Japan) analyzed all biochemical and hematological blood and urine parameters including: GGT, alanine transaminase (ALT), aspartate transaminase (AST), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, total serum protein, albumin, total bilirubin, lactate dehydrogenase, blood urea nitrogen, creatinine, uric acid, sodium, potassium, chloride, blood glucose, white blood cells, red blood cells, hemoglobin, hematocrit and platelets. Urine samples were used for the analysis of

Table I. Demographic and biochemical data for subjects in the placebo and OE groups at entry.

Measurement	Normal range	Placebo group (n=42)	OE group (n=42)	P-value
Age (years)		48.8±9.1	46.3±8.7	0.205
Gender (male/female, n)		31/11	31/11	1.000
Height (cm)		168±8	166±8	0.535
Weight (kg)		67.0±11.9	67.6±11.0	0.817
BMI (kg/m^2)		23.8±2.9	24.3±3.2	0.378
Systolic BP (mmHg)		135±18	132±14	0.428
Diastolic BP (mmHg)		85±10	83±11	0.427
Heart rate (beats/min)		74±10	76±10	0.386
LDL-cholesterol (mg/dl)	65-139	124±38	129±43	0.570
HDL-cholesterol (mg/dl)	40-85	65±18	64±17	0.684
TG (mg/dl)	30-149	167±132	157±104	0.718
GGT (IU/l)	10-50	78.1±29.5	78.3±30.7	0.974
ALT (IU/l)	5-45	28.0±15.4	30.4±14.4	0.475
AST (IU/l)	10-40	25.8±7.2	26.1±10.1	0.842

Data are presented as the mean ± standard deviation with the exception of gender. The P-value refers to the between-group difference assessed by Student's unpaired t-test for all parameters with the exception of gender and by the χ^2 test for gender. OE, oyster extract; BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; GGT, γ-glutamyltransferase; ALT, alanine transaminase; AST, aspartate transaminase.

qualitative protein, qualitative glucose, qualitative occult blood, urobilinogen and pH.

Anthropometrics and hemodynamics. Height was measured at the beginning of the study. Body weight was measured and BMI calculated at weeks 0, 4, 8 and 12. Systolic and diastolic blood pressures (BP) were measured, with subjects in the sitting position following 10 min rest, using an automatic sphygmomanometer.

Statistical analysis. Data are presented as the mean ± standard deviation. Only data from subjects completing the study were included in the efficacy analysis. The baseline characteristics of the randomized subjects were compared between the placebo and OE groups by Student's unpaired t-test and the χ^2 test for mean values and proportions of parameters, respectively. Between-group comparisons of efficacy results were performed by comparing the changes from baseline (week 0) that were calculated by subtracting the initial (week 0) value from the value at each prescribed assessment time-point (weeks 4, 8 and 12) between the placebo and OE groups with the use of Student's unpaired t-test. Within-group differences of group means were compared by Student's paired t-test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of subjects. Eighty-four individuals were enrolled in the study and assigned to either the placebo or OE group (each n=42; 31 males and 11 females). Table I shows the baseline data for the randomized subjects expressed as group mean in the placebo and OE groups. At enrollment, there were no significant differences in the values of any anthropometric, hemodynamic and biochemical parameters between the two groups. It is also shown in this table that the mean baseline levels of all parameters including the liver enzymes ALT and AST, with the exception of the liver enzyme GGT, for the two groups were within the normal range or marginally increased above it.

Four of the 84 enrolled subjects [placebo group (n=2; 2 males) and OE group (n=2; 1 male and 1 female)] dropped out of the study during weeks 1-4 for personal reasons unrelated to the study, and thus 80 subjects completed the study, giving a retention rate of 95%. The ingestion rate of allocated products in all individual subjects was >86.9% with the average value being 99.2%. Six subjects were excluded from efficacy analysis for the following reasons: i) >2-fold increase in GGT level compared with the baseline (≥200 IU/l, probably due to excessive alcohol intake [n=3; 1 female (placebo group)] and 2 males (OE group)]; ii) insufficient alcohol intake in frequency (3.6 to 4.5 times per week on average) compared with 5-7 times for requirement [n=3; 1 female (placebo group) and 2 males (OE group)]. Thus, 38 subjects (29 males and 9 females) in the placebo group and 36 (26 males and 10 females) in the OE group were subjected to efficacy analysis.

Effect on GGT and other liver enzymes. As shown in Table II, the mean baseline (week 0) GGT, ALT and AST activities were not statistically different between the placebo and OE groups. During the 12-week intervention, the GGT activity tended to elevate gradually in the placebo group, being increased by 12% compared with the activity at week 0 (88.5 versus 79.3 IU/l, respectively), although the change in the activity of the enzyme did not reach statistical significance (P=0.077). By contrast, GGT levels appeared to be reduced

Table II. Liver enzyme activity during the 12-week intervention in the placebo (n=36) and OE groups (n=38).

		Week 4		Week 8		Week 12	
Enzyme	Week 0 activity	Activity	P-value	Activity	P-value	Activity	P-value
GGT (IU/l)							
Placebo	79.3±29.5	77.5±35.7 (-2%)	0.701	80.5±37.8 (2%)	0.768	88.5±41.8 (12%)	0.077
OE	76.9±32.0	71.7±30.7 (-7%)	0.278	74.5±28.2 (-3%)	0.583	70.6±30.5 (-8%)	0.290
ALT (IU/l)							
Placebo	28.7±15.9	27.0±12.7 (-2%)	0.388	26.5±12.8 (-8%)	0.358	31.4±20.2 (9%)	0.348
OE	31.0±15.1	27.2±13.0 (-12%)	0.071	29.9±15.6 (-4%)	0.471	27.5±13.6 (-10%)	0.058
AST (IU/l)							
Placebo	25.9±7.3	24.8±5.3 (-4%)	0.310	25.4±6.0 (-2%)	0.728	26.4±8.0 (2%)	0.745
OE	25.5±7.7	23.8±7.2 (-7%)	0.101	25.6±10.6 (0%)	0.966	22.9±6.8 (-10%)	0.168

Activity data are presented as the mean ± standard deviation. Percentage changes (presented in the brackets) are from week 0. The statistical significance of a within-group difference in measurement from week 0 was assessed by the Student's paired t-test. OE, oyster extract; GGT, γ-glutamyltransferase; ALT, alanine transaminase; AST, aspartate transaminase.

Table III. Alcohol intake in subjects of the placebo and OE groups (g/day).

Group	Weeks 1-4	Weeks 5-8	Weeks 9-12	Weeks 1-12
Placebo (n=36)	54±29	54±28	52±27	53±27
OE (n=38)	47±24	46±28	47±28	47±25
P-value	0.222	0.188	0.446	0.250

Data are presented as the mean ± standard deviation. The P-value refers to the between-group difference assessed by the Student's unpaired t-test. OE, oyster extract.

throughout the intervention period in the OE group, whose mean value at week 12 was 8% lower than that at baseline. However, the reduction in values was not statistically significant (70.6 versus 76.9 IU/l, respectively; P=0.290).

Fig. 1 shows the comparison of changes from baseline in the mean value of GGT at weeks 4, 8 and 12 between the placebo and OE groups. There was a significant difference between the placebo and OE groups at week 12 (mean change from baseline: placebo, 9.2±31.1 IU/l; OE, -6.3±35.4 IU/l; P<0.05) but not at weeks 4 and 8.

A similar trend showing an increase and decrease in activity in the placebo and OE groups, respectively, was also seen for ALT and AST; however, there was no significant within-group or between-group differences at any time-point during the intervention period (Table II, Fig. 1).

Alcohol intake analysis. Self-reported intake of alcohol is presented in Table III. No difference was observed in the mean alcohol intake between the placebo and OE groups at any assessment time-point throughout the study period.

Safety and tolerability. The OE supplement, as well as the placebo, used in this study was well tolerated. No subject withdrew due to adverse events. Only 3 of the 42 subjects (7%) in the OE group and 12 of the 42 subjects (29%) in the placebo group reported minor adverse events. The most prevalent adverse events were the common cold (2 in the OE group and 4 in the placebo group), being followed by gastrointestinal upset (4 in the placebo group). It is noteworthy that 2 cases in the placebo group but none in the OE group had hangovers. These self-recorded adverse events were mild in intensity, occurred only temporarily and were judged by the investigator as not associated with the treatment. In both study groups, routine laboratory tests (with the exception of GGT) and measurements of anthropometric and hemodynamic parameters did not show any clinically significant abnormalities throughout the intervention.

Discussion

The present pilot randomized, double-blind, placebo-controlled study was conducted to evaluate the effect of an OE supplement on liver enzymes in individuals with an alcohol drinking habit who had slightly increased GGT activities. The effectiveness of the OE supplement in improving alcohol-deteriorated liver function was shown by the results of an efficacy assessment based on liver enzymes, particularly the GGT results. In the OE group, serum GGT levels were significantly reduced compared with those in the placebo group after 12 weeks of intervention (P<0.05).

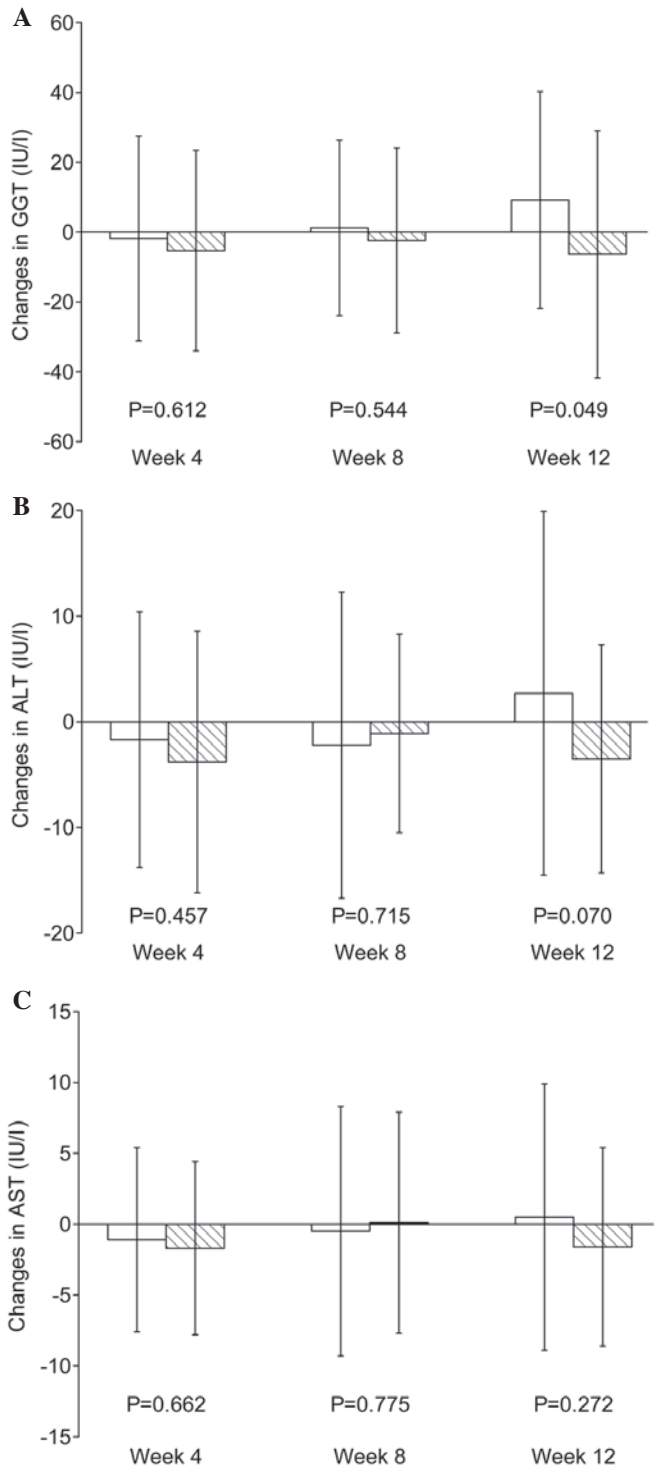

Figure 1. Comparison of changes in serum levels from the value at week 0 of (A) GGT, (B) ALT and (C) AST to the value at weeks 4, 8 and 12 during the 12 week intervention between the placebo group (open bars; n=36) and the OE group (diagonally striped bars; n=38). Data are presented as the mean ± standard deviation. The P-value refers to the between-group difference assessed by Student's unpaired t-test. OE, oyster extract; GGT, γ-glutamyl transferase; ALT, alanine transaminase; AST, aspartate transaminase.

Although ALT and AST levels also appeared to be improved by the OE supplement consumption, there was no significant between-group difference in these two liver enzymes. This can be explained by the fact that baseline mean values of ALT and AST in both groups were within the normal range. Furthermore, GGT has been found to be the most sensitive and specific marker of alcoholic liver injury and excessive alcohol consumption (17-19,22-24). It is, therefore, considered that the majority of the subjects in the present study were at an early stage of development of ALD, such as hepatic steatosis. Alcoholic steatosis is a reversible disorder, and the reduction of steatosis is reported to arrest the progression of ALD (25). These findings and the data showing that there is no difference between the two groups in the estimated alcohol consumption throughout the study period, indicate that a reduction in GGT by OE supplement is likely to be due to an improvement in alcoholic liver injury.

The efficacy of OE in reducing the serum level of liver enzymes (ALT, AST and/or GGT) has been demonstrated in an animal model of ALD (25), in humans with mild alcoholic liver injury (26,27) and those with chronic hepatitis (28). Consistent with these reports, the present study performed with individuals who had an alcohol drinking habit and a slightly raised GGT showed that OE supplement consumption was effective in decreasing serum GGT levels. Regarding the underlying mechanism of the hepatoprotective action of OE, Ming *et al* (29) reported that supplementation with OE significantly suppressed the elevation of serum levels of alcohol and acetaldehyde in rats receiving alcohol. This led them to the suggest that OE is effective in enhancing alcohol metabolism catalyzed by various hepatic enzymes in the alcohol dehydrogenase pathway (29).

The constituents of OE that are active in hepatoprotection remain to be defined; however, we suggest that taurine may be the major active component for the following reasons: i) The OE preparation for the OE supplement product used in the present study contains a substantial amount of taurine (>5%, w/w); ii) numerous animal studies have demonstrated that hepatic injury due to chronic alcohol administration can be ameliorated by treatment with taurine (13-16,30-32); and iii) there are several other common biological activities, particularly hepatoprotection-associated lipid and anti-oxidative activities, shared by OE (33,34) and taurine (6,12).

Throughout the 12-week intervention with the OE supplement at a daily dose of 1,000 mg (>50 mg as taurine), no untoward side-effects were reported and no abnormalities of any anthropometric parameters or in laboratory test results were observed. The safety of the OE supplement is supported by a previous toxicological study performed with rats showing that there were no significant toxic effects nor any interaction with various therapeutic medicines, such as anti-platelet aggregation drugs (e.g., aspirin) and anti-blood coagulation drugs (e.g., warfarin), following 90-day administration at a daily dose of 1,000 or 2,000 mg/kg (35). In humans, it is known that the main source of taurine is diet, the amount of daily taurine intake is estimated to range from 40 to 400 mg (36), and that excess taurine is inert and is excreted into the urine unchanged (37).

Based on all the data obtained from this study, it may be concluded that an OE supplement can be safely administered and is effective in improving alcohol-impaired liver function in subjects with an alcohol-drinking habit. Thus, an OE supplement could be a potential candidate for preventing alcoholic liver injury.

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