Original Article

Effect of Gamma-oryzanol-enriched Rice Bran Oil on Triglyceride Levels and TG/HDL Ratio in the Patients with Hypertriglyceridemia: Double-Blind Randomized Clinical Trial

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Background: Hypertriglyceridemia may contribute to hardening or thickening of the artery walls which increases the risk of stroke and heart disease. Therefore, the normal level of serum triglyceride can prevent both cardiovascular and cerebrovascular diseases. Gamma-oryzanol, a phytosterol compound presents in rice bran oil, has been shown to exhibit lipid-lowering effects in both animals and human.

Objective: To evaluate the effect of gamma-oryzanol-enriched-rice bran oil from Thai brown rice, prepared by innovation technology, on plasma triglyceride (TG) level in patients with hypertriglyceridemia.

Materials and Methods: Double-blind randomized clinical trial was carried out in 54 subjects with hypertriglyceridemia. They were divided into two groups (27 patients per group) and treated with RBOh (gamma-oryzanol-enriched rice bran oil, 20,000 ppm of gamma-oryzanol), and RBOn (cooking oil, gamma-oryzanol 5,000 ppm). The treatments were performed for 8 weeks. Physical examinations and laboratory tests were performed at weeks 0 (as baseline), 4th and 8th of the study. Lifestyle modifications were conducted in both groups.

Results: Significant reduction of plasma TG levels at the 4th and 8th weeks of the treatment were found in RBOh-treated group with *p*-value = 0.024 and 0.006, respectively. In RBOn-treated group, significant reduction of plasma TG and increase in HDL levels and was observed at the 4th week, but not the 8th week of the treatment, with *p*-value = 0.001 and 0.020, respectively. TG/HDL cholesterol ratio was significantly reduce at the 4th and 8th week in RBOh-treated group (*p*-value = 0.011 and 0.048, respectively) and at the 4th week in RBOn-treated group (*p*-value = 0.003). No serious side effects were found throughout the study period in any group of treatment.

Conclusion: Rice bran oil containing gamma oryzanol could reduce the TG level in hypertriglyceridemic patients. The RBOh, gamma oryzanol-enriched rice bran oil, showed prominent effects in reducing serum TG level and TG/HDL ratio. Therefore, RBOh intakes might be able to help prevent the occurrence of cerebrovascular and cardiovascular disease in the patients with hypertriglyceridemia.

Keywords: Hypertriglyceridemia, Rice bran oil, Gamma-oryzanol, TG/HDL ratio

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Hypertriglyceridemia is certainly a prevalent risk factor for cardiovascular disease (CVD), stroke and even pancreatitis. In addition, hypertriglyceridemia is also increasingly important in the setting of current obesity and insulin resistance epidemics. At the present, it is confidence to conclude that TG levels and triglyceride/high density lipoprotein cholesterol ratio, appear to provide unique information as a biomarker of CVD risk because of their association with atherogenic lipoproteins and apolipoproteins and may contribute to hardening of the arteries or thickening of the artery walls and leading to myocardial infarction and eventually the patient's death[1-5]. Rice bran oil (RBO), extracted from the hard outer brown layer of rice (rice bran), is known to provide healthy fats and a variety of other beneficial nutrients, including gamma oryzanol (γ-OR), phenolic acid, polyphenol, flavonoid, vitamin E and multi phytosterols[6]. The researches and studies over 50 years have found RBO, especially γ-OR, can reduce blood total cholesterol, triglyceride and LDL-C, and increase HDL-C[7-9]. The National Cholesterol Education Program (NCEP) suggested for the treatment of patient with hyperlipidemia, first step is changing the life-styles and

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food consumption[10]. RBO is the one of vegetable oil recommended to take for the reduction of lipid blood levels. In Thailand market, there is one RBO product developed by innovation technology containing quite high concentration of γ-OR (approximately 20,000 ppm). It is interesting to see whether the gamma oryzanol-enriched RBO could have beneficial effect in patients with hypertriglyceridemia. The aim of this study was to evaluate the triglyceride lowering effects of gamma-oryzanol-enriched rice bran oil, prepared by innovation technology, comparison with cooking oil in Thai patients with hypertriglyceridemia.

Materials and Methods

Study design

This study was an 8-weeks double-blind randomized clinical trial conducted from June 2019 to April 2020, at the Out-Patients Department, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand. The study protocol was approved by the Ethic Committee for Human Research, Panel 1, Khon Kaen University) (HE621060), Thailand. All patients have to give their informed consent before enrollment in this study. The primary outcome was the reduction of serum triglyceride level, compared between two RBO products, gamma-oryzanol 20,000 ppm (RBOh) and 5,000 ppm (RBOn). The sample size was calculated by stata 10 software to be 23 subjects were needed in each group. Calculation an overall dropout rate of 15%, the patients per group of 27, and total patient number in this study was 54.

Study subjects

All subjects were eligible if they met the following criteria: 1) male or female aged 20 to 60 years, and 2) serum triglyceride level ≥150 to 300 mg/dL. The subject were excluded if: 1) impaired renal or hepatic function (creatinine >1.17 mg/dL in male or >0.95 mg/dL in female or ALT-alanine transaminase (0 to 33 U/L), AST-aspartate transaminase (0 to 44 U/L) more than 2.5 time over the upper normal level), 2) history of oil allergy, 3) poor control of systemic disease such as stage III hypertension, fasting plasma glucose >250 mg/dL, HbA1c >8 mg%, cardiovascular disease and pancreatitis, 4) pregnancy or lactation period, 5) current treatment with lipid lowering agents.

Study procedures

All the enrolled subjects were received physical examinations (weight, height, blood pressure, heart rate) and checked for blood chemistry (serum lipid profile, fasting plasma glucose, HbA1C, creatinine, ALT, and AST) as baseline data. The enrolled subjects were randomly assigned using a block of two, to RBOh or RBOn at the dose of 15 ml/day daily for 8 weeks. They were informed regarding lifestyle modification at all visits during the trial. The subjects came to the clinic at 4th and 8th week post treatment for an assessment about blood parameter, physical examination, and adverse events were performed. There were no restrictions on the intake of co-medication for underlying diseases. Each patient also completed the SF-36 questionnaire (Thai version) to evaluate their quality of life at the end of clinical trial.

Intervention

Gamma-oryzanol-enriched rice bran oil (RBOh) and cooking oil (RBOn) used in this study were provided as gifts from Medifoods company (manufacturing standard GMP NOP HACCP GREEN INDUSTRY, Bangkok, Thailand), each product prepared from the same lot number.

Treatment outcomes

The effective primary outcome was the reduction of serum triglyceride level and TG/HDL ratio at 4th and 8th weeks post treatment when compared to the baseline.

Safety monitoring

Adverse effect was evaluated by physical examination and blood chemistry for liver and renal functions at the beginning and the 4th and 8th weeks of the study period. Each subject also completed the intervention with another sign and symptom that developed or become worse from baseline to the end of study.

Statistical analysis

All statistical analysis was performed using stata statistical software version 10 under the license of KKU. The result variables were expressed as mean ± SE, mean difference and 95% confidence interval (95% CI). Data within group and between groups were compared using before and after student's pair t-test. All analysis used the level of statistic significant *p*-value <0.05.

Results

Demographic and other baseline characteristic of study patients

A total of 54 eligible patients were randomly assigned to receive RBOh or RBOn formulas. 27 patients in RBOh group were 10 males, and 17 females, average ages of the subject were 49.52 years, and average BMI was 27.44. The RBOn group were 16 males, and 11 females, average ages of the subject were 53.04 years, and average BMI was 26.04. Most common characteristic of them were occasional exercise, no smoking and no alcohol drinking. Underlying disease compost of diabetes mellitus, hypertension, allergy, and co-medication were glucose lowering (glibenclamide, metformin, insulin) and antihypertensive (amlodipine, enalapril). After 4th weeks of the clinical study, 4 patients were withdrawn because of nausea and vomiting (3 patients in RBOh group, 1 patient from RBOn group), and 4 patients of unknown cause of loss to follow-up at 8th weeks (2 patients in RBOh group, 2 patients from RBOn group). 6 patients have been poor compliance for RBO intake (2 patients in RBOh group, 4 patients from RBOn group), forty patients enrolled completed in the clinical study, 20 in RBOh, and 20 in RBOn group. Characteristics of the study subjects were summarized in Table 1

Table 1. Baseline characteristic and demographic data of the patients

Variables	RBOh (27)	RBOn (27)
Age (years) (mean ± SE)	49.52±10.65	53.04±8.08
Gender: male/female (n, %)	10 (37)/17 (63)	16 (59.3)/11 (40.7)
Body Mass Index ($kg.m^{-2}$) (mean ± SE)	27.44±4.41	26.04±3.02
Systolic blood pressure (mmHg ±SE)	137.93±2.88	137.59±3.75
Diastolic blood pressure (mmHg ±SE)	82.89±2.31	84.7±2.76
Heart rate (beat/min±SE)	80.04±1.97	76.37±1.56
FPG (mg/dL ±SE)/HbA1c (mg% ±SE)	114.96±7.07/6.66±0.31	112.89±9.9/6.42±0.29
Creatinine (mg/dL) ±SE	0.91±0.05	0.91±0.03
ALT (U/L) ±SE	27.3±3.05	30.22±5.18
AST (U/L) ±SE	29.37±5.88	28.66±5.14
Smoking habit (n, %)		
Non-smoking	23 (85.2)	23 (85.2)
Ex-smoker	3 (11.1)	2 (7.4)
Current smoker	1 (3.7)	2 (7.4)
Alcohol drinking (n, %)		
Non-drinking	20 (74.1)	20 (74.1)
Ex-drinking	6 (22.2)	7 (25.9)
Current drinking	1 (3.7)	0
Exercise (n, %)		
Non-exercise	6 (22.2)	5 (18.5)
Occasional	15 (55.5)	18 (66.7)
Habits	6 (22.2)	4 (14.8)
Underlying disease	16 (59.3) *	12 (44.4)
DM	6	4
DLD	3	1
HT	7	3
Allergic rhinitis	3	2
Other; gout, PU, hypothyroidism	3	2
Co-medication		
Sulfonylurea	0	2
Metformin	0	2
Regular insulin	1	0
Amlodipine	3	0
Enalapril	2	1
Other; hydralazine, doxazocin	0	2
Colchicine	1	0

* = some patients have more than one underlying disease
ALT = alanine transferase, AST = aspartate transferase, DM = diabetes mellitus, DLD = dyslipidemia, HT = hypertension, PU = peptic ulcer

Efficacy outcome

Effects of RBO on serum lipid level in hypertriglyceridemic patients were shown in Table 2 and Figure 1. When compared to the baseline values, subjected received RBOh showed a significant reduction of serum triglyceride level at the end of the 4th and 8th weeks (p-value = 0.024 and 0.006, respectively). In the group treated with RBOn, a significant decrease of serum triglyceride only at the 4th week (p-value = 0.001), and increase in HDL-C levels at the end of the 4th week (p-value = 0.020)

Table 2. Effect of RBO on plasma lipid level of hypertriglyceridemia patients

Variables	RBOh (20)	RBOn (20)
Triglyceride (mg/dL)		
Baseline (week 0)	187.90±6.53	213.58±9.83
Post 4 weeks	160.20±11.61	178.63±9.26
Mean difference (w0-4)/95% CI	27.70±1.329/3.99, 51.41	34.947±9.013/16.01, 53.88
p-value	0.024*	0.001*
Post 8 weeks	151.65±10.65	188.84±16.91
Mean difference (w0-8), 95% CI	36.25±11.75/11.67, 60.83	24.74±15.25/-7.30, 56.77
p-value	0.006*	0.122
Cholesterol (mg/dL)		
Baseline (week 0)	207.45±9.93	209.30±5.80
Post 4 weeks	206.200±9.60	211.00±7.04
Mean difference (w0-4)/95% CI	1.25±5.13/-9.486, 11.986	-1.70±6.01/-14.28, 10.88
p-value	0.810	0.780
Post 8 weeks	206.400±7.97	206.80±5.28
Mean difference (w0-8), 95% CI	1.05±6.63/-12.82, 14.92	2.50±5.46/-8.93, 13.93
p-value	0.876	0.365
LDL-C (mg/dL)		
Baseline (week 0)	153.40±10.79	153.95±6.69
Post 4 weeks	153.60±10.17	158.15±7.06
Mean difference (w0-4)/95% CI	-0.20±4.98/-10.62, 10.22	-4.20±6.70/-18.21, 9.81
p-value	0.968	0.538
Post 8 weeks	148.95±8.45	146.90±5.75
Mean difference (w0-8), 95% CI	4.45±6.52/-9.20, 18.10	7.05±5.94/-5.39, 19.49
p-value	0.503	0.250
HDL-C (mg/dL)		
Baseline (week 0)	47.30±1.99	47.84±1.96
Post 4 weeks	48.30±2.26	51.58±2.66
Mean difference (w0-4)/95% CI	-1.00±1.98/-5.14, 3.14	-3.74±1.47/-6.83, 0.65
p-value	0.619	0.020*
Post 8 weeks	46.80±1.69	49.21±2.21
Mean difference (w0-8), 95% CI	0.5±1.91/-3.50, 4.50	-1.37±1.31/-4.13, 1.39
p-value	0.797	0.311
TG/HDL-C		
Baseline (week 0)	4.12±0.24	4.67±0.35
Post 4 weeks	3.324±0.28	3.70±0.31
Mean difference (w0-4)/95% CI	0.79±0.28/0.20, 1.38	0.97±0.28/0.38, 1.55
p-value	0.011*	0.003*
Post 8 weeks	3.40±0.32	4.09±0.45
Mean difference (w0-8), 95% CI	0.72±0.34/0.01, 1.43	0.58±0.424/-0.31, 1.47
p-value	0.048*	0.187

were seen. A significant reduction of TG/HDL ratio was seen at the end of 4th and 8th weeks (*p*-value = 0.011 and 0.048, respectively) in RBOh-treated patients and at the end of 4th week (*p*-value = 0.003) in RBOn-treated patients

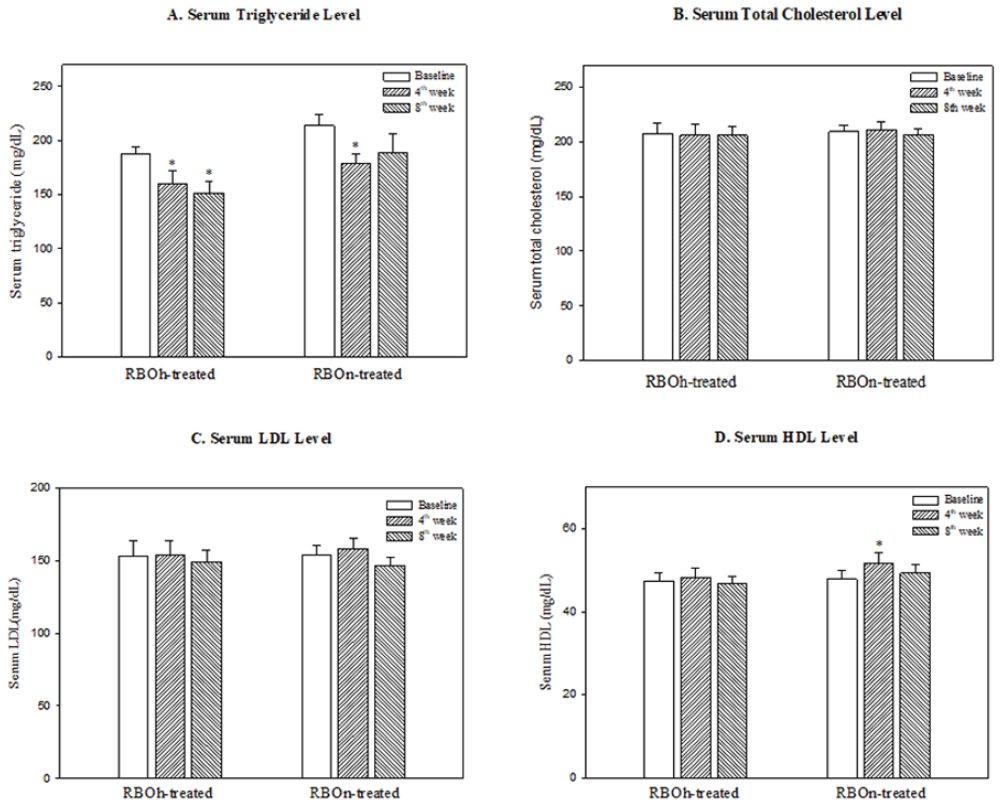

Figure 1. Effects of RBOh and RBOn on TG (A), cholesterol (B), LDL (C), and HDL (D) at the 4th and 8th weeks of interventions.

(Figure 2). No significant effect of on hemoglobin A1C, blood sugar, and other observed parameters could be seen. During the period of intervention, no distinct side effect was reported, except some patients were withdrawn from the experiment since they had nausea and vomiting when eat oil.

Concerning the effect of the intervention on quality of life (QoL), all of them have high score of QoL, and no significant difference between groups. In addition, some positive subjective feelings such as gastrointestinal functions, good quality of sleep, knee joint function, bright skin, and thicker of hair were recorded from either treatment groups.

Safety and tolerability

Adverse events (AEs) reported in 4 patients in RBO intervention were nausea and vomiting; 3 (11.11%) patient in RBOh group, and another 1 (3.7%) in RBOn group. At the end of the 8th weeks, 4 patients from both groups were lost follow-up for unknown reasons (2 patients in RBOh group, and 2 patients in RBOn group). There were no differences of ALT, AST, and creatinine level in any of treatment group. All reported AEs was mild in severity and self-limited solving. Overall, all patients were well tolerated and they were no clinical changes in blood chemistry or vital signs.

Discussion

This randomized clinical trial, gamma-oryzanol-enriched rice bran oil showed a significant reduction in serum triglyceride level after 4 and 8 weeks of intake. Our findings confirm that the consumption of rice bran oil can help lower serum triglyceride[7-13]. There have been several studies focused on the role of γ-OR, major phytosterol in rice bran oil, in reducing serum lipid levels. It has been suggested that γ-OR and its metabolite (ferulic acid), are responsible for the lipid lowering effect of rice bran oil[6,14,15]. A significant reduction in cholesterol absorption, alteration of lipid metabolism modulation, and decreasing of lipid synthesis were observed after RBO intake[7,16]. However, no effect on serum cholesterol concentration of patients enrolled in this trial could be observed and this may be caused by the normal cholesterol levels of the patients. The effects of γ-OR on triglyceride level are suggested to be involved

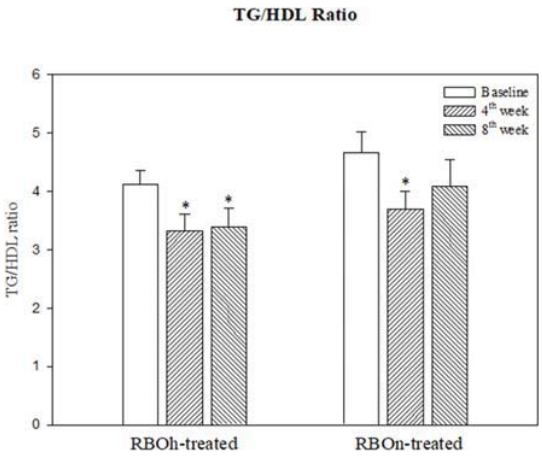

Figure 2. Effects of RBOh and RBOn on TG/HDL ratio at the 4th and 8th weeks of interventions.

with various mechanisms, including interference with fatty acid absorption within the intestinal lumen, modulation of hepatic de novo lipogenesis and reduction in circulating medium and large VLDL particles[17]. In addition, inhibition of hepatic triglyceride synthesis, decrease VLDL synthesis and secretion, and increased serum lipoprotein lipase activity are also suggested[18,19]. These effects lead to the reduction of total cholesterol, LDL-C, apolipoprotein, triglyceride, and induction of HDL-C[7,9]. In our study, RBO from Thai brown rice with very high concentration of γ-OR showed a persistent significant effect in reducing serum triglyceride level throughout the intervention period, suggests that high γ-OR level is needed in controlling triglyceride level in patients with hypertriglyceridemia.

It is interesting to note that γ-OR-enriched rice bran oil could reduce TG/HDL level significantly at both the 4th and 8th weeks of intervention. Recently, TG/HDL ratio is a marker of small/dense LDL particles, which believed to be very closely associated with various metabolic and vascular diseases, including cardiovascular and cerebrovascular diseases[20]. It has been reported that TG/HDL-C ratio is a powerful predictor of total mortality independent of important prognostic variables including age, race, smoking, hypertension, diabetes, and severity of coronary artery diseases[21], especially women with a TG/HDL-C ratio of 3.66 or higher[21]. At both the 4th and 8th weeks of treatment, TG/HDL ratio in RBOh-treated group were lower than 3.6, this might suggest the beneficially effect of γ-OR-enriched rice bran oil in reducing the prevalence and burden of various metabolic and vascular diseases.

Conclusion

The results of this study indicated that γ-OR-enriched rice bran oil derived from Thai brown rice could be useful as a functional food to improve health in general population, especially hyperlipidemia group who having high blood triglyceride level; guidance with life-style modification. In addition, these γ-OR-enriched rice bran oil derived from Thai brown rice might help control and reduce the risks of many diseases linked with metabolic syndromes. However, our findings should be confirmed with further studies in a larger number of patients in each group.

What is already known on this topic?

RBO has been lowering of total cholesterol, triglyceride, LDL-C, and increase HDL-C in animal and human. This study is the first study investigating the triglyceride-lowering of a γ-OR-enriched rice bran oil derived from Thai brown rice by innovation technique, comparison of cooking oil (gamma-oryzanol 5,000 ppm) and gamma-oryzanol-enriched rice bran oil (gamma-oryzanol 20,000 ppm) in the hypertriglyceridemic patients who were undergoing life-style modification.

What this study adds?

The result showed that γ-OR-enriched (20,000 ppm) rice bran oil derived from Thai brown rice could reduction of triglyceride level and TG/HDL ratio in hypertriglyceridemic patients. γ-OR-enriched rice bran oil derived from Thai brown rice might be used as a nutraceutical or functional food in the patients with hypertriglyceridemia who were undergoing with life-style modification and diet control.

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Conflicts of interest

The authors declare no conflict of interest.

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