

# Antihyperlipidemic Effects of Red Ginseng, Crataegii Fructus and Their Main Constituents Ginsenoside Rg3 and Ursolic Acid in Mice

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**Abstract** – Anti-hyperlipidemic effect of red ginseng (RG; the steamed root of *Panax ginseng* C.A. Meyer) and Crataegii fructus (CF, the fruit of *Crataegus pinnatifida* BGE), which are used frequently in China and Korea as herbal medicines to treat arteriosclerosis, were investigated. Treatments of RG and CF significantly reduced blood triglyceride (TG) and total cholesterol (TC) levels in Triton WR-1339-induced hyperlipidemic mice and serum TG levels in corn oil-induced hypertriglyceridemic mice. Ginsenoside Rg3 and ursolic acid, the main constituents of RG and CF, respectively, also reduced TG and TC levels in hyperlipidemic mice. RG and CF significantly lowered the high blood TG and TC levels and body and epididymal mass weights induced by long-term feeding of a high-fat diet and increased the high-fat diet-induced decrease in blood HDL cholesterol levels. RG and Rg3 reduced the blood TC levels more than CF and ursolic acid. However, blood TG level were reduced by CF and ursolic acid more than RG and Rg3. RG, CF, and their constituents also inhibited pancreatic lipase and HMG-CoA reductase activities. The most potent inhibitor was Rg3. These findings suggest that RG and CF may be suitable for the therapies of hypercholesterolemia and triglyceridemia, respectively.

**Keywords:** Red ginseng, *Crataegus pinnatifida*, Hyperlipidemia, Pancreatic lipase, HMG-CoA reductase, Ginsenoside Rg3, Ursolic acid

## INTRODUCTION

Lipid metabolism normally maintains an elegant balance between synthesis and degradation. When this balance is lost, hypercholesterolemia and hyperlipidemia may develop, leading to arteriosclerosis, hypertension, obesity, diabetes, and functional depression of select organs (Goldstein *et al.*, 1973). The rate-limiting enzyme of cholesterol biosynthesis from acetate is HMG-CoA reductase (Heller and Shrewsbury, 1976; White and Rudney, 1970). Pancreatic lipase is a key enzyme for lipid breakdown and fatty acid absorption (Birari and Bhutani, 2007). Inhibitors of pancreatic lipase or HMG-CoA reductase are anti-hypercholesterolemic agents (Birari and Bhutani, 2007; Endo *et al.*, 1992; Davidson, 2003), such as orlistat and lovastatin, and reduce the absorption of dietary triglycerides and inhibit cholesterol biosynthesis, respectively. However, repeated use of these agents

causes side effects (Davidson, 2003; Ballinger, 2000). Thus, herbal medicines have been receiving increased attention as alternative treatments for hyperlipidemia (Zhou *et al.*, 2005).

Red ginseng (RG), which is the steamed root of *Panax ginseng* CA Meyer, showed hypolipidemic effects in cyclophosphamide- and Triton WR-1339-induced mice (Trinh *et al.*, 2007; Inoue *et al.*, 1999). Its main ingredients, the ginsenosides Rg3 and Rh2, reduced blood TG and TC levels in triton WR-1339-induced hyperlipidemic mice (Trinh *et al.*, 2007). Crataegii fructus (CF, the fruit of *Crataegus pinnatifida* BGE) also showed antihyperlipidemic effects in rats and humans (Chang *et al.*, 2005; la Cour *et al.*, 1995). Its main constituent, ursolic acid, reduced blood TC levels in experimental arteriosclerosis in rats and rabbits (Liu, 1995). Nevertheless, their antihyperlipidemic mechanism has not been thoroughly studied.

Therefore, to understand their antihyperlipidemic effects, we investigated the hypolipidemic effects of RG, CF, and their main constituents, ginsenoside Rg3 and ursolic acid, on corn oil, Triton WR-1336 and high fat-induced experimental hyperlipidemic mice.

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## MATERIALS AND METHODS

### Materials

Triton WR-1339, tributyrin, PL, ursolic acid, and lovastatin were purchased from Sigma Chemical (St. Louis, MO, USA). Total cholesterol and triglyceride assay kits were purchased from Asan Pharmaceutical Co. Ltd. (Korea). Orlistat (Xenical) was kindly donated by Dr. B W Song of Kyung Hee Medical Center, Kyung Hee University (Seoul, Korea). A high-fat diet containing 25% beef tallow [American Institute of Nutrition (AIN)-76 fat-diet #180337] was purchased from Dyets, Inc. (Bethlehem, PA, USA).

RG and CF were purchased from Kyung Dong Market (Seoul, Korea) and identified by Dr. Nam-Je Kim, East-West Medical Research Institute, Kyung Hee Medical Center, Kyung Hee University. The ginsenoside, Rg3, was isolated from RG as previously described (Trinh *et al.*, 2007).

### Extraction of RG and CF

RG (500 g) or CF (500 g) were extracted twice with 5 L of boiling water, filtered, evaporated in a rotary vacuum evaporator, and freeze-dried. The yields were 23.9%, 20.2%, and 22.3%, respectively. The main component of each extract was analyzed using a Younglin HPLC system (Younglin instrument, Korea). The sample extracts were subjected to Develosil C30-UG-5 (4.6 × 250 mm, 5 μm, Nomura Chem. Co. Ltd., Japan). The mobile phase was water (solvent A) and acetonitrile. Gradient elutions were performed as follows: solvent B increasing from 0% to 100% in 20 min and then held at 100% for 5 min. The injected volume was 20 μL, the flow rate was 1 mL/min, and the UV absorbance was monitored at 203 nm. The contents of ursolic acid in CF extract and Rg3 in RG extract were 0.68% and 0.27%, respectively.

### Assay of PL activity

The enzyme activity assay was performed according to a previously reported method. (Bae *et al.*, 2002). The reaction mixture (3.06 mL) contained 135 mM triolein emulsified in gum acacia, 2 mM sodium thioglycolate, and PL (0.6 U using triacetin as a substrate), adjusted to pH 8.8 with 0.1 M NaOH, incubated at 25°C, and adjusted to pH 8.8 with 10 mM NaOH. The inhibitory activity of the sample was calculated from the titrated volume.

### Assay of HMG-CoA reductase activity

HMG-CoA reductase was partially purified according to the method of Edwards *et al.* (1980). Male Sprague-Daw-

ley rats (250-300 g body weight) were housed one per cage in a room where the lights were off from 7:00 AM to 7:00 PM. Food and water were available *ad libitum*. For 3 days prior to killing, the rats were fed powdered rat chow containing 5% cholestyramine. Animals were killed at 1:00 PM, the peak of the HMG-CoA reductase cycle. The livers were homogenized at 4°C in 25 mL buffer A (0.1 M sucrose, 0.05 M KCl, 0.04 M potassium phosphate, and 0.03 M potassium EDTA; pH 7.2) with a motor-driven, tight-fitting, glass-Teflon Potter-Elvehjem homogenizer, and microsomes were prepared. Three-milliliter aliquots of the microsomal suspension were frozen in glass tubes at a rate of 6-8°C per min unless otherwise stated, and stored at -20°C for up to 2 months. For optimal solubilization of the reductase, the frozen microsomes were allowed to thaw to 37°C before addition of an equal volume of 50% glycerol in buffer B (buffer A plus 10 mM DTT) preheated to 37°C. The suspension was rehomogenized with 10 downward passes of a hand-driven, all-glass Potter-Elvehjem homogenizer and then incubated at 37 °C for 60 min. The suspension was diluted three-fold with buffer B heated to 37°C for a final glycerol concentration of 8.3%, rehomogenized with 10 downward passes of the glass homogenizer pestle, and centrifuged at 100,000 × g for 60 min at 25°C. The supernatant containing solubilized HMG-CoA reductase was used for the enzyme inhibitory activity assay as the crude enzyme.

The inhibitory activity assay of HMG-CoA reductase was performed according to the method of Edwards *et al.* (1979). Its activity was determined at 37°C in a total volume of 0.5 mL using a Beckman spectrophotometer (Shimazu). The cell path length was 1.0 cm. The oxidation rate of NADPH was initially determined in the absence of HMG-CoA, and this blank value was subtracted from the rate obtained with both substrates. The activity assay reaction mixture contained 0.2 M KCl, 0.16 M potassium phosphate, 0.004 M EDTA, and 0.001 M DTT, 0.2 mM NADPH, and 0.1 M RS-HMG-CoA; pH 6.8.

### Animals

Male ICR mice (20-25 g) were purchased from Orient Charles River Co. (Korea) and fed a commercial diet (Orient Charles River Co., Korea). These animals were kept for at least 7 days prior to the experiments. All animals were housed in wire cages at 20-22°C, 50% ± 10% humidity, fed standard laboratory chow (Samyang, Seoul, Korea), and allowed water *ad libitum*. All procedures relating to animals and their care conformed to the international guidelines 'Principles of Laboratory Animals Care' (NIH publication no. 85-23 revised 1985).

To evaluate hypolipidemic effects, three kinds of hyperlipidemic animal models were established. First, a hyperlipidemic mouse model based on corn oil was established according to the method of Duhault *et al.* (1976). Six mice were used per group. Corn oil (1 g/kg) was orally administered 2 h after each sample was administered orally. Two hours after the administration of corn oil, blood samples of the mice were drawn by cardiac puncture under ether anesthesia. Second, a hyperlipidemic mouse model based on Triton WR-1339 was established according to the method of Kusama *et al.* (1988). Triton WR-1339 was injected at the end of the regular 16 h fasting period as a 10% solution in saline at a dose of 200 mg/kg body weight into the tail veins of mice under light ether anesthesia. Six mice were used per group. These mice were anesthetized with ether 18 h after Triton WR-1339 injection, and 1-1.5 mL of blood was drawn by cardiac puncture. Sera were obtained by centrifugation (1500 × g, 10 min). Tested samples, lovastatin or Xenical, were administered orally once a day for 3 days before Triton WR-1339 injection. The final administration of the samples was performed 1 h before Triton WR-1339 injection. Third, a hyperlipidemic mouse model based on high-fat diets was established. Mice were classified into 15 groups. Each group contained 6 mice. The high-fat control group was fed a high-fat diet for 5 weeks. The normal group received a solid, normal diet. CF and RG were orally administered for 5 weeks at 50 mg/kg/day, ursolic acid and the ginsenoside Rg3 at 20 mg/kg/day, and xenical at 10 mg/kg/day. After a 16 h fasting period following the final administration of samples, blood samples were drawn by cardiac puncture under ether anesthesia.

#### Determination of serum total cholesterol, triglyceride, and HDL cholesterol

Total cholesterol was measured by the enzymatic method of Allain *et al.* (1974). Serum triglycerides were measured by the method designed by Kim *et al.* (2008). HDL cholesterol was measured by the enzymatic method of Kim *et al.* (2008).

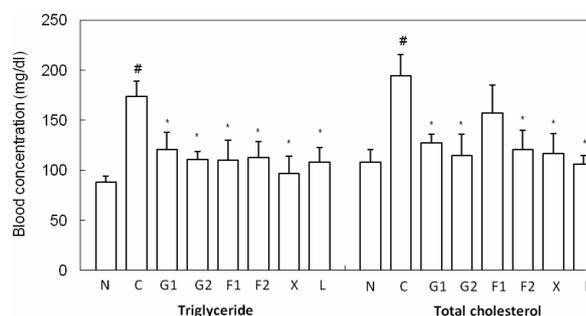
#### Statistical analysis

All data are expressed as the mean ± standard deviation, and statistical significance was analyzed by Student's *t*-test.

## RESULTS

#### *In vivo* antihyperlipidemic activity of RG and CF

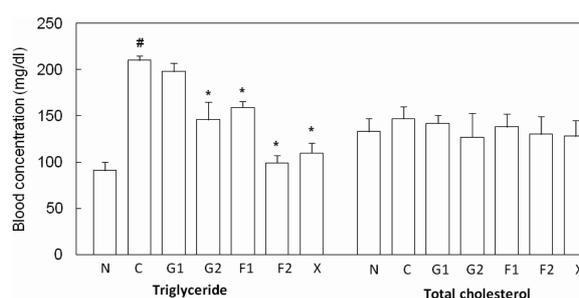
We measured the hypolipidemic effects of RG and CF



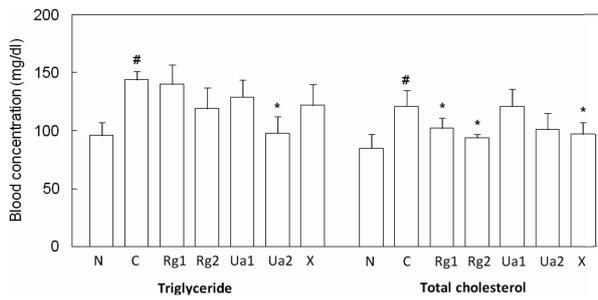
**Fig. 1.** Effect of red ginseng (RG), and Crataegii fructus (CF) in Triton WR-1339-induced Hyperlipidemic Mice. The normal group (N) received a vehicle alone. The control group (C) was treated with Triton WR-1339 alone. The samples were orally administered with Triton WR-1339: G1, 50 mg/kg red ginseng; G2, 100 mg/kg red ginseng; F1, 50 mg/kg Crataegii fructus; F2, 100 mg/kg Crataegii fructus; X, 10 mg/kg Xenical; L, 10 mg/kg lovastatin. Values indicate mean ± S.D. (n=6). # Significantly different, compared with normal group ( $p < 0.05$ ). \*Significantly different, compared with control group ( $p < 0.05$ ).

on Triton WR-1339-induced hyperlipidemic mice (Fig. 1). Serum triglyceride (TG) and total cholesterol (TC) levels increased after treatment with Triton WR-1339. Treatment with RG or CF significantly reduced the Triton WR-1339-induced increases. RG more potently reduced TC levels than CF, but CF more potently reduced TG levels than RG.

We also measured the inhibitory effects on corn-oil-induced hyperlipidemic mice (Fig. 2). Corn oil feeding significantly induced serum triglyceride levels, but not cho-



**Fig. 2.** Hypolipidemic Effect of red ginseng (RG), and Crataegii fructus (CF) in Corn Oil-induced Hyperlipidemic Mice. The normal group (N) received a vehicle alone. The control group (C) was treated with corn oil alone. The samples were orally administered with corn oil: G1, 50 mg/kg red ginseng; G2, 100 mg/kg red ginseng; F1, 50 mg/kg Crataegii fructus; F2, 100 mg/kg Crataegii fructus; X, 10 mg/kg Xenical. Values indicate mean ± S.D. (n=6). # Significantly different, compared with normal group ( $p < 0.05$ ). \*Significantly different, compared with control group ( $p < 0.05$ ).

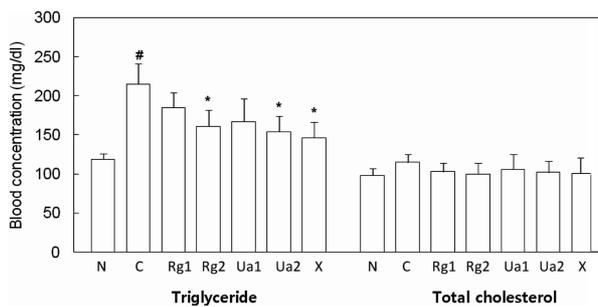


**Fig. 3.** Hypolipidemic Effect of Ginsenoside Rg3 and Ursolic Acid on Triton WR-1339-induced Hyperlipidemic Mice. The normal group (N) received a vehicle alone. The control group (C) was treated with Triton WR-1339 alone. The samples were orally administered with Triton WR1339: Rg1, 10 mg/kg ginsenoside Rg3; Rg2, 25 mg/kg ginsenoside Rg3; Ua1, 10 mg/kg ursolic acid; Ua2, 25 mg/kg ursolic acid; X, 10 mg/kg Xenical. Values indicate mean ± S.D. (n=6). # Significantly different, compared with normal group (p<0.05). \* Significantly different, compared with control group (p<0.05).

lesterol levels. RG and CF treatment reduced serum TG levels, but not back to control levels. CF was more potent than RG.

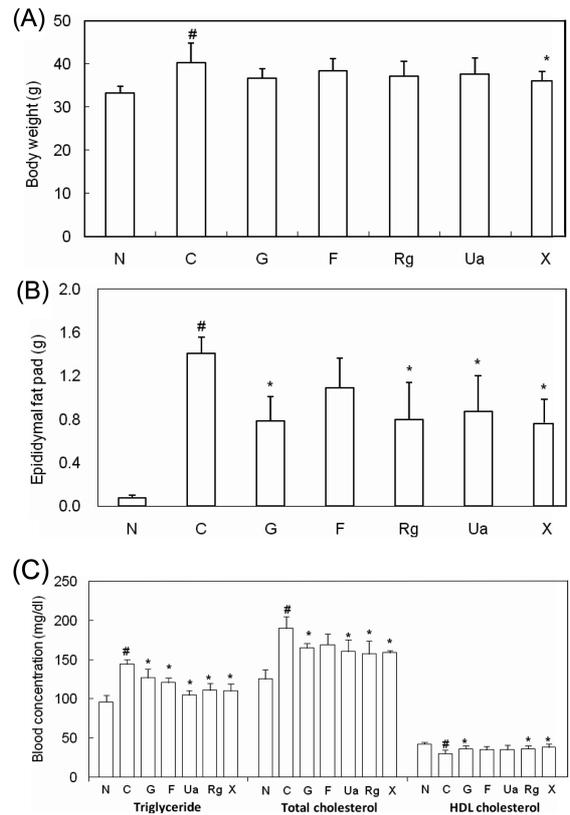
**In vivo antihyperlipidemic activity of Rg3 and ursolic acid**

We measured the inhibitory activities of a representative component of RG, Rg3, and a representative comursolic acid, in Triton WR-1339-induced hyperlipidemic mice (Fig. 3). TG and TC levels in serum were increased



**Fig. 4.** Hypolipidemic Effect of Ginsenoside Rg3 and Ursolic Acid on Corn Oil-induced Hyperlipidemic Mice. The normal group (N) received a vehicle alone. The control group (C) was treated with corn oil alone. The samples were orally administered with corn oil: Rg1, 10 mg/kg ginsenoside Rg3; Rg2, 25 mg/kg ginsenoside Rg3; Ua1, 10 mg/kg ursolic acid; Ua2, 25 mg/kg ursolic acid; X, 10 mg/kg Xenical. Values indicate mean ± S.D. (n=6). # Significantly different, compared with normal group (p<0.05). \* Significantly different, compared with control group (p<0.05).

by treatment with Triton WR-1339, with Rg3 and ursolic acid treatment reducing those elevations. The TG level in the ursolic acid-treated group (25 mg/kg) was decreased more than in the Rg3-treated group, whereas Rg3 treatment reduced TC more than ursolic acid treatment. Rg3 and ursolic acid treatment also reduced hyperlipidemia levels in the corn oil treated group (Fig. 4). TG levels in the ursolic acid-treated group (25 mg/kg) were decreased more than the Rg3-treated group.



**Fig. 5.** Effect of red ginseng (RG), and Crataegii fructus (CF) on Body (A) and Epididymal Fat (B) Weights and Serum Triglyceride, Total cholesterol and High Density Lipoprotein (HDL) Cholesterol Levels (C) in Hyperlipidemic Mice Induced by High-Fat Diets. Each group contained 6 mice with body weights of 24.3 ± 0.93 g (mean ± standard deviation) per a mice. The normal group (N) received a normal, solid diet. The control group (C) was fed the high-fat diet for 5 weeks, respectively. These agents were orally administered once a day with the high-fat diet for 5 weeks: G, 50 mg/kg red ginseng; F, 50 mg/kg Crataegii fructus; Rg, 20 mg/kg ginsenoside Rg3; Ua, 20 mg/kg ursolic acid; X, 10 mg/kg Xenical. Body weight was measured before the final administration of the samples. Epididymal fat pads were taken under ether anesthesia and their weights were measured. Values indicate mean ± S.D. # Significantly different, compared with normal group (p<0.05). \* Significantly different, compared with control group (p<0.05).

**Table 1.** Inhibitory Effect of Red Ginseng (RG), *Crataegii Fructus* (CF), Ginsenoside Rg3 and Ursolic Acid for Pancreatic Lipase and HMG CoA Reductase Activities

Samples	IC <sub>50</sub>	IC <sub>50</sub>
	Pancreatic lipase (mg/ml)	HMG CoA reductase (mg/ml)
RG	1.8	2
CF	1.6	5
Ursolic acid	0.9 (1.7) <sup>a)</sup>	0.6 (1.1)
Ginsenoside Rg3	1.5 (2.1)	0.2 (0.3)
Xenical	0.8 (1.6)	0.2 (0.4)

<sup>a)</sup>Values in parenthesis are those indicated in mmole for pancreatic lipase and  $\mu$ mole for HMG CoA reductase.

### Effect of long-term feeding of RG and CF on high-fat diet-induced hyperlipidemia in mice

We next measured the hypolipidemic effects of long-term feeding of RG, CF, and their constituents, Rg3 and ursolic acid, on high-fat diet-induced hyperlipidemic mice (Fig. 5). Triglyceride and total cholesterol levels in serum were increased by treatment with a high-fat diet for 5 weeks. RG, CF, and their constituents significantly decreased these levels. Ursolic acid (20 mg/kg) reduced TG levels the most potently, followed by Rg3 (20 mg/kg), and CF (50 mg/kg). Rg3 (20 mg/kg) reduced TC levels the most potently, followed by ursolic acid (20 mg/kg) and RG (50 mg/kg). These agents also were most potent at reducing the body and epididymal mass weights induced by the high-fat diet. Of them, RG most potently inhibit its increment.

### *In vitro* inhibitory effect of RG, CF, and their constituents on pancreatic lipase and HMG-CoA reductase activities

To understand the hypolipidemic mechanism of RG and CF, we measured their inhibitory effects on pancreatic lipase and HMG-CoA reductase (Table 1). RG and CF all inhibited pancreatic lipase with similar potencies. However, their potencies against HMG-CoA reductase activity were different, with Rg3 the most potent, with an IC<sub>50</sub> value of 2.1 mg/mL (triolein as a substrate), followed by ursolic acid and RG.

## DISCUSSION

Hyperlipidemia can cause arteriosclerosis, hypertension, obesity, diabetes, and functional organ depression (Goldin et al., 1973). To cure hyperlipidemia, the inhibi-

tors against pancreatic lipase, which is a key enzyme in lipid breakdown and is required to absorb fatty acids (Thomson *et al.*, 1993), and HMG-CoA reductase, which catalyzes a key step in the mevalonate pathway, which is involved in the synthesis of sterols, isoprenoids, and other lipids (Espenshade and Hughes, 2007; Meigs *et al.*, 1996) have been developed.

Xenical and statins have been developed. However, the repeated used of orlistat and lovastatin results in side effects (Davidson, 2003; Ballinger, 2000; Thompson Coon and Thompson Coon and Ernst *et al.*, 2003). Therefore, many researchers have been studying the hypolipidemic effects of herbal medicines to develop them as alternative treatments for hyperlipidemia. However, the antihyperlipidemic effects of RG and CF have not been thoroughly studied. Here, RG and CF, as well as their constituents had antihyperlipidemic effects on corn oil-, Triton WR1339- and high-fat diet-induced hyperlipidemic mice. RG more potently reduced total blood cholesterol levels than CF, whereas CF more potently reduced total triglyceride levels than RG. The ginsenoside Rg3 and ursolic acid, the primary constituents of RG and CF, also potently reduced blood total cholesterol and triglyceride levels. Compared with the parent agents, Rg3 more potently reduced total cholesterol levels, and ursolic acid more potently reduced total triglyceride levels. The inhibitory effect of Rg3 is comparable with that of lovastatin, which is a potent inhibitor for HMG-CoA reductase. The inhibitory effect of ursolic acid is comparable with that of Xenical, which is a potent inhibitor for pancreatic lipase.

In hyperlipidemic mice induced by long-term feeding of high fat, RG and CF and their constituent lowered blood total cholesterol and triglyceride levels as well as body and epididymal mass weights. Particularly, RG and Rg3 reduced total blood cholesterol levels more than ursolic acid; however, ursolic acid lowered blood triglyceride levels more than Rg3. RG and CF all inhibited pancreatic lipase and HMG CoA reductase activities. CF and its constituent ursolic acid more potently inhibited pancreatic lipase activity than RG. RG and its constituent Rg3 more potently inhibited HMG-CoA reductase activity than ursolic acid, which is a main constituent of CF. These results suggest that the antihyperlipidemic effect of RG, particularly the ginsenoside Rg3, may be due to inhibition of HMG CoA reductase rather than pancreatic lipase, and that the effects of CF, particularly ursolic acid, may be due to inhibition of pancreatic lipase more than HMG-CoA reductase. These findings suggest that RG and CF

may be suitable for the therapies of hypercholesterolemia and triglyceridemia, respectively.

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