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*Full Length Research Paper*

# Study of antihyperlipidemic effect on rabbits of 8-alkylberberine derivatives

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**To study the antihyperlipidemic effect of 8-alkyl-berberine derivatives (8-BBR-$C_n$). The experimental hyperlipidemia rabbits were prepared by feeding with high cholesterol and high fat (HCHF) diet. Then the effects of 8-alkyl-BBR on the serum levels of total cholesterol (TC), triglyceride (TG), (HDL-C), low density lipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C) in rabbit blood were measured and those on hepatic and kidney function were observed. 8-BBR-$C_n$ effectively decreased the serum content of TC, TG, LDL-C and increased HDL-C level in hyperlipidemic rabbits, compared with berberine. The antihyperlipidemic effect was increased with elongating the alkyl chain of 8-BBR-$C_n$. Among all synthesized derivatives, 8-cetyl-berberine (8-BBR-$C_{16}$) showed the highest antihyperlipidemic effect, which was a dose-effect relationship on blood lipid. Pathological examination indicated that 8-BBR-$C_{16}$ could recover the liver tissue of rabbits damaged by high lipid diet. 8-BBR-$C_{16}$ showed a strong antihyperlipidemia effect with low toxicity, thus it might be a promising drug of antihyperlipidemic.**

**Key words:** Berberine (BBR), 8-alkyl-berberine derivatives (8-BBR-$C_n$), antihyperlipidemic effect.

## INTRODUCTION

Berberine (BBR) is the major active ingredient of *Rhizoma coptidis*, which has anti-bacterium (Sack and Froehlich, 1981), antihyperglycemia (Tang et al., 2006), antihyperlipidemia (Yin et al., 2003), anti-heart failure (Zeng et al., 2003) functions. BBR has been mainly used for acute gastroenteritis, bacillary dysentery, furuncle, suppurative otitis media, conjunctivitis in clinical therapeutics at present (Wang et al., 1993). What is more important, BBR isolated form *Coptis chinensis* showed the highest activity in increasing LDLR expression among 700 Chinese herbs (Kong et al., 2004). The structure–activity relationship of berberine analogues revealed substituted derivatives at the position in A, C or D-ring of quaternary protoberberine alkaloids led to the change in its pharmacological effect (Iwasa et al., 1999; Hong et al., 2000). Methenedioxyl replacement at C-2 and C-3 positions, 8-alkyl or 13-alkyl substitution increased the antibacterial activity (Hong et al., 2000; Iwasa et al., 1998).

The antimicrobial activity of the 8-alkyl and 13-alkyl-substituted berberines increased with the aliphatic chain elongating, 8-alkyl-substituted berberines showed stronger antimicrobial activity than the 13-alkyl-substituted berberines, and showed that the introduction of hydrocarbon groups at position C-8 increased the antimicrobial activity (Iwasa et al., 1998). The antimicrobial activity of 8-alkylberberine and 3-O-alkyhizine-derivatives increased with the aliphatic chain elongating and then decreased gradually when the alkyl chain start exceeding eight carbon atoms (Yang et al., 2007; Wang et al., 2008), however 13-hydroxyl substitution decrease the antibacterial activity (Iwasa et al., 1996). The study on antibacterial activity and structure-activity relationship of berberine derivatives provided a new way for seeking other pharmacological

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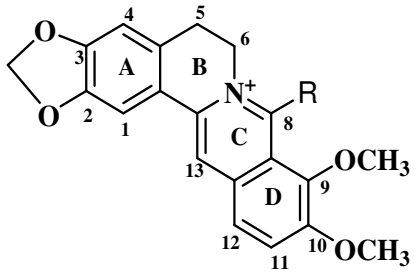


$R=C_nH_{2n+1}$; n=0, 2, 4, 6, 8, 10, 12, 16

**Figure 1.** Structure of 8-alkyl-berberine derivatives.

activity of the compounds.

To improve the poor adsorption of berebrine *in vivo*, 8-BBR-$C_n$ derivatives (n=0, 2, 4, 6, 8, 10, 12 and 16) (Figure 1) were synthesized in our laboratory by introducing different length alkyl chain at $C_8$ position (Yang et al., 2007). Our previous study showed that the $LD_{50}$ of alkylated derivatives increased with the elongation of alkyl chain (Yang et al., 2007), which may had an improved antihyperlipedemic activity. In this study, the hyperlipidemic rabbit model was obtained by gavaging high cholesterol and high fat diet, the lipid modulating effects and hepatorenal function of 8-BBR-$C_n$ were investigated to evaluate the antihyperlipidemic effect of 8-BBR-$C_n$, and to further obtain novel prodrugs with high antihyperlipidemic activity and safety.

## MATERIALS AND METHODS

### Materials

Lovastatin and Berberine Hydrochloride (Ber) were respectively bought from Beijing HongHui Bio-pharmaceutical Co, Ltd (Beijing, China) and Mian yang High-tech Zone Dong Fang Yuan Bio-tech Co, Ltd, (Chendu, China). 8-Alkylberberine derivatives (8-Ber-$C_n$) (Yang et al., 2007) were provided by School of Pharmaceutical School, Southwest University (Chongqing, China), including 8-ethyl (8-BBR-$C_2$), 8-butyl (8-BBR-$C4_n$), 8-hexyl (8-BBR-$C_6$), 8-octyl (8-BBR-$C_8$), 8-decyl (8-BBR-$C_{10}$), 8-lauryl (8-BBR-$C_{12}$) and 8-cetyl-berberine chloride (8-BBR-$C_{16}$). The kits for TC, TG, LDL-C, HDL-C, ALT, TBIL, Cr, BUN were purchased from Nanjing Jiancheng Biological Co, Ltd (Nanjing, China), and measured with an EOS BRAVO Full-auto Clinical Chemistry Analyzer (HOSPITEX DIAGNOSTIC s.rll., Italy). Cytometry was measured by the CD1700 Blood cell analyzer (Abbott Laboratories. USA).

### Animals

Male New Zealand rabbits (2.0 to 2.5 kg, 75 to 90 days old) were purchased from Animal Breeding Center of the Third Military Medical University (Chongqing, China). Healthy SD rats of both genders (130~140 g, 7 weeks old, SPF grade) were purchased from the Laboratory Animal Centre of Chongqing Medical University (Animal certificate No. 0001802, and license No. scxk (Yu) 20020004). The regular and high cholesterol and high fat (HFHC) diets containing 1% cholesterol, 3% lard and 6% yolk powder were from Animal Breeding Center of the Third Military Medical University.

### Antihyperlipidemia effect of BBR and 8-BBR-$C_n$

Male New Zealand rabbits were housed in a stainless cage with controlled temperature (23 ± 2°C) and humidity (40 to 60%) and a 12 h light/dark cycle. After 1 week of accommodation period, six rabbits were fed with the regular rabbit diet serving as normal diet controls. Other animals were fed with HFHC diet for 15 days to prepare the hyperlipidemic rabbits. After the rabbits were fed with HFHC diet for 15 days, the blood lipid levels were measured. Those rabbits whose triglyceride (TG) and total cholesterol (TC) were up to 8.0 and 2.0 $mmol.L^{-1}$ respectively, were chosen as the hyperlipidemic rabbits. Then hyperlipidemic rabbits were untreated or treated with 4 mg/Kg per day of Lovastatin, or 15 mg/Kg per day of berberine or its derivative orally for 40 days (each group containing 6 rabbits), respectively. 3 ml compounds suspended in steriled physiological saline were orally administered to the animals by gavage once a day at 8 a.m. Following parameters were used for comparative analysis: (1) Blood samples were collected from the ear vein of each rabbit and centrifuged to obtain sera.

Then serum levels of TC, TG, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), alanine aminotransferase (ALT), total bilirubin (TBIL), blood urea nitrogen (BUN), creatinine (Cr) were measured. (2) Body weight was measured by electro balance at 10-day intervals.

The criteria to evaluate the damages of histopathological examination were carried out according to the literature (Fatty Liver and Alcoholic Liver Disease Study Group of Chinese Liver Disease Association, 2003). In subsequent experiment, in order to observe the dose-dependent effect of the optimal compounds screened according to the lipid-lowering result, the hyperlipidermic rabbits were untreated or treated with compound 4F at low dosage (5 mg/Kg per day ), medium dosage (10 mg/Kg per day) or high dosage (15 mg/Kg per day), respectively for 40 days. Then, blood lipid levels and hepatorental function including ALT, TBIL, BUN and Cr were assayed.

### The long-term toxicity of 8-BBR-$C_{16}$

In order to show the long term toxicity of 8-BBR-$C_{16}$, healthy SD rats of both genders were housed in stainless cages in a room with controlled temperature (23 ± 2°C) and humidity (40 to 60%) and a 12 h light/dark cycle to observe their general conditions such as food-intake, behavioral activity and stool. Body weight was measured at 15 days intervals, and the drug dosage was adjusted timely according the body weight.

Animals were randomly divided into 4 groups with 20 rats each. At the end of the treatment period, all animals were killed, blood samples were collected by cutting rats' tails for hematological and biochemical examinations; samples of heart, liver, spleen, pancreas and kidney were collected for organ coefficients (organ coefficients = organ weight / Body weight x 100%) and histopathological examination.

The protocol complied with the guidelines of Chongqing City Laboratory Animal Administration Committee of China for the care and use of laboratory animals.

### Statistics

The data was analyzed by SPSS11.5 software and expressed as mean ± standard deviation (SD) and one-way analysis of variance (ANOVA) was used for statistical evaluation. Differences were accepted as statistically significant at P values <0.05.

**Table 1.** Effect of 8-BBR-$C_n$ on lowering-lipid efficiency in rabbit (n=6, mean±SD).

| Group | Dose | TC | TG | LDL-C | HDL-C |
|---|---|---|---|---|---|
| | mg.kg$^{-1}$ | mmol.L$^{-1}$ | mmol.L$^{-1}$ | mmol.L$^{-1}$ | mmol.L$^{-1}$ |
| Normal control | — | 1.29 ± 0.25 | 0.72 ± 0.25 | 1.75 ± 0.24 | 0.80 ± 0.24 |
| Hyperlipidemic control | — | 8.89 ± 0.53$^{\#\#}$ | 2.11 ± 0.43$^{\#\#}$ | 3.45 ± 0.56$^{\#\#}$ | 0.67 ± 0.22$^{\#}$ |
| Lovastatin | 4 | 2.56 ± 0.38$^{**}$ | 1.62 ± 0.42$^{*}$ | 1.85 ± 0.33$^{**}$ | 0.78 ± 0.21$^{*}$ |
| BBR | 15 | 7.94 ± 0.65 | 2.02 ± 0.33 | 3.27 ± 0.30 | 0.70 ± 0.23 |
| 8-BBR-$C_2$ | 15 | 7.76 ± 0.67 | 2.03 ± 0.57 | 3.29 ± 0.56 | 0.70 ± 0.26 |
| 8-BBR-$C_4$ | 15 | 7.41 ± 0.64 | 2.01 ± 0.64 | 3.21 ± 0.34 | 0.71 ± 0.34 |
| 8-BBR -$C_6$ | 15 | 7.26 ± 0.60 | 2.00 ± 0.60 | 3.27 ± 0.44 | 0.71 ± 0.14 |
| 8-BBR -$C_8$ | 15 | 6.25 ± 0.65$^{*}$ | 1.95 ± 0.65 | 3.06 ± 0.52 | 0.70 ± 0.32 |
| 8-BBR -$C_{10}$ | 15 | 6.04 ± 0.72$^{*}$ | 1.86 ± 0.72 | 2.98 ± 0.45 | 0.72 ± 0.25 |
| 8-BBR -$C_{12}$ | 15 | 6.02 ± 0.61$^{*}$ | 1.73 ± 0.61 | 2.41 ± 0.42$^{*}$ | 0.73 ± 0.22 |
| 8-BBR -$C_{16}$ | 15 | 2.22 ± 0.36$^{**}$ | 1.58 ± 0.39 | 2.02 ± 0.44$^{**}$ | 0.75 ± 0.26 |

$^{\#}P< 0.05$ $^{\#\#}P< 0.01$ vs normal control group; $^{*}P< 0.05$ $^{**}P< 0.01$ vs Hyperlipidemic control group.

**Table 2.** Dose-effect relationship of 8-BBR-$C_{16}$ (n=6, mean±SD).

| Group | Dose | TC | TG | LDL-C | HDL-C |
|---|---|---|---|---|---|
| | mg.kg$^{-1}$ | mmol.L$^{-1}$ | mmol.L$^{-1}$ | mmol.L$^{-1}$ | mmol.L$^{-1}$ |
| Normal control | — | 1.34 ± 0.22 | 0.74 ± 0.27 | 1.74 ± 0.27 | 0.79 ± 0.02 |
| Hyperlipidemic control | — | 8.74 ± 0.53$^{\#\#}$ | 2.07 ± 0.33$^{\#\#}$ | 3.47 ± 0.44$^{\#\#}$ | 0.69 ± 0.02$^{\#}$ |
| 8-BBR -$C_{16}$ (low dosage) | 5 | 6.92 ± 0.43$^{*}$ | 1.95 ± 0.33 | 2.67 ± 0.28$^{*}$ | 0.70 ± 0.01 |
| 8-BBR -$C_{16}$ (medium dosage) | 10 | 4.26 ± 0.46$^{**}$ | 1.89 ± 0.40 | 2.46 ± 0.22$^{*}$ | 0.72 ± 0.03 |
| 8-BBR -$C_{16}$ (high dosage) | 15 | 2.48 ± 0.23$^{***}$ | 1.25 ± 0.37 | 2.15 ± 0.24$^{**}$ | 0.75 ± 0.02 |

$^{\#}P< 0.05$ $^{\#\#}P< 0.01$ vs normal control group; $^{*}P< 0.05$ $^{**}P< 0.01$ vs Hyperlipidemic control group.

## RESULTS

### Effects of different 8-alkylberberine derivatives on lipid profile in rabbits

All the rabbits kept in good health status and survived the experimental period. There were no significant differences in the body weights among different groups during the period of the whole experiment (P>0.05). The levels of TC, TG, LDL-C and HDL-C in hyperlipidemic control group were remarkable differences (P<0.05 or 0.01), compared with the normal control group. After 40 days administration, atorvastatin treated group and 8-BBR-Cn groups could decrease the content of TC, TG and LDL-C in blood of rabbits in different degree and increase that of HDL-C in blood of hyperlipidemic rabbits. The content TC, TG and LDL-C decreased with the carbon chain elongation of 8-BBR-Cn. Compared with the group of hyperlipidemic control, the levels of TC in 8-BBR-C8, 8-BBR-C10, 8-BBR-C12 group were significantly reduced (P<0.05), and those of TC, LDL-C in 8-BBR-C16 group were very significantly reduced (P<0.01). It indicated that 8-BBR-C16 showed the best lipid-lowering effect (Table 1).

### Dose-effect relationship of 8-BBR-C16

The levels of TC, TG, LDL-C and HDL-C in hyperlipidemic control group were remarkable differences (P<0.05 or 0.01) compared with the normal control group. After40-day administration of 8-BBR-C16, TC, LDL-C levels in every dose group of 8-BBR-C16 treated group were significantly reduced compared with the hyperlipidemic control group group(P<0.05 or 0.01), and the degrees of reduction of TC and LDL-C in the high dose group showed more evident than the other dose groups. Although the levels of TG, HDL-C in every dose group were improved as compared to the hyperlipidemic control group, there were no statistical significance (P>0.05) (Table 2).

### The effect of 8-BBR-$C_{16}$ on the hepatorenal function

Effect of 8-Ber-$C_{16}$ on hepatorenal function was shown in (Table 3). After administration of 8-Ber-$C_{16}$ for 40 days, the levels of ALT, TBIL, Cr and BUN of the hyperlipidemic control group were significant increase as compared to the normal control group. Compared with the

**Table 3.** Effect of 8-BBR-$C_{16}$ on hepatorenal function (n=6, mean±SD).

| Groups | ALT | TBIL | Cr | BUN |
|---|---|---|---|---|
| | $U.L^{-1}$ | $Umol.L^{-1}$ | $mmol.L^{-1}$ | $mmol.L^{-1}$ |
| Normal control | 60.34 ± 13.5 | 12.54 ± 4.51 | 78.06 ± 8.95 | 4.32 ± 0.69 |
| Hyperlipidemic control | 92.14 ± 14.3$^{\#}$ | 28.45 ± 11.55$^{\#}$ | 126.26 ± 14.16$^{\#}$ | 7.25 ± 1.46$^{\#}$ |
| 8-BBR -$C_{16}$ (low dosage) | 82.36 ± 7.03 | 15.56 ± 4.13$^{*}$ | 83.42 ± 8.65$^{*}$ | 5.45 ± 1.16$^{*}$ |
| 8-BBR-$C_{16}$ (medium dosage) | 71.53 ± 6.04$^{*}$ | 13.27 ± 4.53$^{*}$ | 80.26 ± 7.42$^{*}$ | 4.73 ± 1.42$^{*}$ |
| 8-BBR -$C_{16}$ (high dosage) | 64.63 ± 9.2$^{*}$ | 12.82 ± 4.18$^{*}$ | 80.01 ± 10.20$^{*}$ | 4.36 ± 0.42$^{*}$ |

$^{\#}P< 0.05$ $^{\#\#}P< 0.01$ vs normal control group; $^{*}P< 0.05$ $^{**}P< 0.01$ vs Hyperlipidemic control group.

hyperlipidemic control group, the levels of TBIL, Cr, BUN in every dose group were significantly decreased (P<0.05), ALT levels were significantly decreased (P<0.05) except for the low dose group of 8-Ber-$C_{16}$ treated group.

### Long term toxicity of 8-BBR-$C_{16}$

There was no abnormal signs found in the rats during the 90 days oral administration of 8-cetyl-berberine, and their body weights did not show significant statistically changes as compared to the normal control group.The organ coefficients of the heart, liver, kidney, spleen and pancreas had no significant difference as compared to the normal control group, and demonstrated that 8-Ber-$C_{16}$ treated group had no evident influence on main organ weight. The indexes of RBC, WBC, LYM, MID, GRAN, PLT, HB in every dosage group were normal, and there were no significant difference as compared to the normal control group.

The levels of the ALT, TBIL, CR and BUN in every dosage group were within the normal range, which were no significant difference as compared to the normal control group. No visible gross changes such as swelling or bleeding were observed in any organ or tissue at autopsy on 90 days after 8-Ber-$C_{16}$ administration. Histopathological examinations of the heart, liver, kidney, spleen and pancreas were performed. No lesions were found in these organs. So the rats that were orally treated with 8-Ber-$C_{16}$ had no obvious effect on the organic tissue morphology.

## DISCUSSION

Hyperlipidemia is one of dangerous factor of cardio-cerebrovascular diseases, inducing essential hypertension, coronary heart disease, cerebral infarction and promoting atherosclerosis (Ma et al., 2006). Current studies revealed that hyperlipidemia had positive relation between the prevalence and mortality of the atherosclerosis and cardio-cerebrovascular diseases, so aggressive lipid-lowering treatment could improve the atherosclerosis and then decreased the prevalence and mortality of coronary heart disease, cerebral infarction and cerebral hemorrhage, etc (Hong et al., 2003). Therefore, seeking after lipid-lowing drugs and studying on antihyperlipidemia therapy have attracted more and more attention (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). Statins and Fibrates are known to be effective agents for treating hyperlipidemia at present, which mainly promote the metabolism of TC and TG, respectively. However, these drugs could cause certain liver toxicity and damage in a long-term administration, and their side effects have been highly emphasized in clinic at present (Liu et al., 2007). Therefore, to find an inexpensive, efficient and nontoxic lowing-lipid drug, we studied the effects of 8-alkylberberine derivatives on hyperlipidemic rabbits.

It was observed that lipid-lowing activity of 8-alkylberberine derivatives increased with the aliphatic chain elongating, and 8-cetyl-berberine (8-BBR-$C_{16}$) possessed significant effects on decreasing serum TC, LDL-C levels as compared to other compounds and the lipid-lowing effects was dose-dependent. Because hyperlipidemia easily complicated with fatty liver and led to liver damage and transaminase disorder, and most lipid-lowing drugs could cause liver toxicity (Zeng et al., 2000). However, 8-BBR-$C_{16}$ had the ability to protect against hepatorenal damage and keep hepatocellular morphology in normal condition and had a beneficial effect on the prevention and treatment of fatty liver. In addition, the study of long-term toxicity showed that 8-cetyl-berberine was safe, and the checking indexes of every item were normal during the experimental period. The lipid-lowing mechanism of 8-alkylberberine derivatives was unclear. The present results revealed that the modification of aliphatic carbon chain at C-8 position might be potential to increase the lipid-lowering activity. The study showed that the change of the lipophilicity of drug molecules could influence the absorption, meta-bolism, body distribution and drug action target *in vivo*, further influence the efficacy (Turdy and James, 2000). Therefore, it is likely that the improvement of lipophilicity might be beneficial to the lipid-lowing activity of berberine derivatives. However, the exact mechanism of 8-alkylberberine might need further to study.

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