

RESEARCH ARTICLE

Effects of *Ginkgo biloba* extracts on pharmacokinetics and efficacy of atorvastatin based on plasma indices

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Abstract

1. *Ginkgo biloba* extract (GBE) is one of the most widely used herbal medicines in the world. It is often administered in combination with statins to treat diseases, especially some nervous system disorders. We aimed to investigate the influences of GBE on pharmacokinetics and efficacy of atorvastatin, which are currently unclear.
2. Sixteen volunteers received a single oral dose of 40 mg atorvastatin, followed by a wash-out period of at least 5 days. Then the volunteers took 360 mg GBE daily for 14 days, followed by a single dose of 40 mg atorvastatin. Serial blood samples obtained over a period of 48 h after atorvastatin ingestion were subjected to determination of atorvastatin plasma concentrations and markers of cholesterol synthesis (lathosterol) and cholesterol absorption (sitosterol).
3. With GBE administration, AUC_{0-48} , $AUC_{0-\infty}$ and C_{max} of atorvastatin were reduced by 14.27% ($p = 0.005$), 10.00% ($p = 0.03$) and 28.93% ($p = 0.002$), respectively; Vd/F and CL/F of atorvastatin were increased by 31.95% ($p = 0.017$) and 6.48% ($p = 0.044$). After 14 days of treatment, GBE has no significant effects on cholesterol-lowering efficacy of atorvastatin.
4. This study suggests that GBE slightly decreases the plasma atorvastatin concentrations, but has no meaningful effect on the cholesterol-lowering efficacy of atorvastatin.

Keywords: *Ginkgo biloba* extract, atorvastatin, Alzheimer's disease, OATP1B1

Introduction

Ginkgo biloba extract (GBE) is one of the most frequently used herbal medicines in the world. It is used to improve memory in patients with Alzheimer's disease, such as management of primary degenerative dementia (Luo 2006). GBE contains two groups of bioactive constituents: ginkgo flavonol glycosides (i.e. quercetin, kaempferol and isorhamnetin) and terpene lactones (i.e. ginkgolides A, B, C, and J and a 15-carbon sesquiterpene termed bilobalide) (Diamond et al. 2000; Jaracz et al. 2004).

Several researchers found that GBE and the terpene trilactones from GBE could induce the expression of drug

metabolizing enzymes and transporters (i.e. CYP3A5, CYP3A4, UDP-glucuronosyltransferase1A1 (UGT1A1), MDR1 and MRP2) *in vitro* (Yeung et al. 2008; Li et al. 2009; Lau et al. 2010). However, another study showed that flavonol aglycones from GBE inhibited CYP3A activity (von Moltke et al. 2004). Our *in vitro* experiments found that ginkgolides B, C significantly increased cell uptake of [³H] estrone-3-sulfate, which is a special substrate of organic anion transporting polypeptide 1B1 (OATP1B1, encoded by *SLCO1B1* gene) (data not shown).

Statins are the inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. They are one

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group of the most widely prescribed medications of cholesterol-lowering agents. Previous studies showed that their use reduced the incidence of Alzheimer's disease (Baigent et al. 2005; Haag et al. 2009). Atorvastatin is one type of statins. It is the substrate of OATP1B1, whose polymorphism had a marked effect on atorvastatin uptake (Kameyama et al. 2005; Pasanen et al. 2007; Lee et al. 2010). In present, several drugs (i.e. rifampin, gemfibrozil, fimasartan and cyclosporine) have been reported to inhibit OATP1B1 transporter activity and increase the plasma concentrations of atorvastatin, thus increase incidence rate of adverse reaction of statins and increase cholesterol-lowering effects (Lau et al. 2007; He et al. 2009; Amundsen et al. 2010; Whitfield et al. 2011; Shin et al. 2011). Atorvastatin has two major active metabolites, 2-hydroxy-atorvastatin acid and 4-hydroxy-atorvastatin acid, which are mainly metabolized by CYP3A (CYP3A4 and CYP3A5) (Lennernas 2003; Park et al. 2008). Co-administration of atorvastatin with inhibitors of CYP3A4 (mibefradil, itraconazole, cyclosporine, erythromycin and clarithromycin) increased serum concentrations of atorvastatin, which may lead to adverse reactions (Bays and Dujovne 1998; Igel et al. 2001; Williams and Feely 2002; Jacobson 2004). Researcher recently found that grapefruit juice, which specifically inhibits intestinal CYP3A4 activity, slightly increased atorvastatin plasma concentrations, but had no meaningful effect on atorvastatin cholesterol-lowering efficacy (Lennernas 2003; Uno and Yasui-Furukori 2006; Reddy et al. 2011). Atorvastatin is also a substrate of several UDP-glucuronosyltransferases (UGTs) and efflux transporter including P-glycoprotein (P-gp) and ATP-binding cassette G2 protein (ABCG2). Their genetic variability significantly affects atorvastatin pharmacokinetics (Prueksaritanont et al. 2002; Goosen et al. 2007; Keskitalo et al. 2008; Riedmaier et al. 2010).

GBE is often administered in combination with statins to treat diseases in elderly patients, especially individuals with Alzheimer's disease. Thus, understanding their drug-drug interaction is crucial to improve drug safety in these patients. But the effect of GBE on statins' pharmacokinetic and therapeutic efficacy remains unclear.

Considering that GBE could induce the expression of CYP3A, P-gp and OATP1B1 *in vitro*, we hypothesize that the plasma concentration of statins and the efficacy may be affected by GBE. In the present study, we aim to investigate the influence of GBE on pharmacokinetics and efficacy of atorvastatin, and identify potential herb-drug interaction between GBE and atorvastatin.

Materials and methods

Subjects

Sixteen healthy volunteers (men; age 24.8 ± 2.9 years; height, 170.1 ± 6.7 cm; weight, 65.2 ± 5.8 kg) were enrolled in the study. This protocol was approved by the Ethics Committee Board of Central South University, Changsha Hunan, China. All the participants provided written

consent before enrolment. All subjects were determined to be healthy by medical history, routine physical examinations, electrocardiography and clinical laboratory testing. All subjects were nonsmokers and were instructed to abstain from any drugs, grapefruit juice, alcohol, caffeine and tea for at least 2 weeks before the study started.

Study design

This study used a two-period, open-label, fixed-sequence design. After an overnight fasting, volunteers received a single oral dose of 40 mg atorvastatin (one 40 mg tablet of Lipitor; Pfizer, Da Lian, China) with water (200 mL). Following a wash-out period of at least 5 days, volunteers took three 40 mg (120 mg) tablet of *Ginkgo biloba* extract (Dr Willmar Schwabe GmbH & Co. Germany) every third day for 14 days. On day 15, another 40 mg atorvastatin was then administered after overnight fasting. Water and meals were allowed 4 h after atorvastatin administration. To determine the concentrations of atorvastatin and its main metabolites in plasma, blood samples were collected into EDTA-containing tubes at 0, 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 34 and 48 h after atorvastatin ingestion.

Plasma markers of cholesterol synthesis (lathosterol) can be used to estimate the activity of hepatic HMG-CoA reductase and to predict low-density lipoprotein-cholesterol (LDL-C) response to atorvastatin, whereas markers of cholesterol absorption (sitosterol) can be used to investigate intestinal cholesterol absorption (Niemi et al. 2005; Pasanen et al. 2008). Lathosterol positively correlates to LDL-C reduction, whereas sitosterol negatively correlates to LDL-C reduction (Hoenig et al. 2010). Therefore, blood samples taken at 0, 2, 4, 6, 12 and 24 h after administration of atorvastatin were subjected to determination of cholesterol, sitosterol and lathosterol concentrations.

Analytical drug assays

Plasma concentrations of atorvastatin and its metabolites (2-hydroxyatorvastatin acid, 4-hydroxyatorvastatin acid, atorvastatin lactone, 2-hydroxyatorvastatin lactone and 4-hydroxyatorvastatin lactone) were measured by a liquid chromatography/tandem mass spectrometry system (Waters, Milford, MA) with electrospray positive ionization mode. Simvastatin was used as the internal standard. The relative concentrations (plasma responses) of atorvastatin metabolites are given in arbitrary units, which are the relative ratio of the peak area of each metabolite to that of the internal standard. The monitored ion transitions were as follows: 559–440 *m/z* for atorvastatin acid and 419.5–199 *m/z* for simvastatin. The sample preparation and analytical methods were described previously (Jemal et al. 1999; Lau et al. 2007). The valid range of analytes was 0.3775–48.3155 ng/mL. The lower limit of quantification for atorvastatin was 0.3775 ng/mL. There was a good linear relationship for atorvastatin calibration curves ($R^2 > 0.994$). The intra- and inter-day coefficients of variation were 10.24% at 0.7549 ng/mL, 10.028% at 6.0394 ng/mL and 8.72% at 48.3155 ng/mL. The extracted

recovery was >70%. The stability tests are suitable for the analysis of large numbers of samples.

Pharmacokinetic analysis

Pharmacokinetic parameters were performed by non-compartment model using Drug and Statistics Software (DAS, version 2.1, Mathematical Pharmacology Professional Committee of China). Peak plasma concentrations (C_{\max}) and the time taken to reach C_{\max} (t_{\max}) were obtained from concentration-time data. The terminal rate constant (K_e) was calculated by regression analysis of the log-linear portion of the concentration-time curve. The terminal half-life ($t_{1/2}$) was estimated as $0.693/K_e$. The area under the plasma concentration-time curves (AUCs) of atorvastatin was calculated using the linear trapezoidal rule. The oral clearance (CL/F) was obtained as follows: $CL/F = \text{dose}/AUC_{0-\infty}$. Apparent volume of distribution (Vd/F) was estimated as $Vd/F = CL/F/K_e$.

Measurement and analysis of cholesterol, lathosterol and sitosterol

Plasma sterol (cholesterol, lathosterol and sitosterol) concentrations were measured by gas chromatography/mass spectrometry (Agilent, Santa Clara, CA), as described in detail previously (Heinemann et al. 1993; Lutjohann et al. 1995; Niemi et al. 2005; Hoenig et al. 2010). 5 α -cholestane was used as the internal standard. The calibration curves of the sterols were linear. The recoveries based on replicate analyses of plasma samples, which were spiked with known amounts of sterol standards, were 89.5–106.3%. Inter-day and intra-day coefficients of variances were <15%. The limits of quantitation of cholesterol, lathosterol and sitosterol were 4.0, 0.13 and 0.16 $\mu\text{g}/\text{mL}$, respectively. The stability tests are suitable for handling of the clinical samples.

The effects of atorvastatin on the rate of cholesterol absorption and cholesterol synthesis were determined by plasma noncholesterol sterols concentration, mean percent change and maximum percent decrease in non-cholesterol sterol to cholesterol ratios (Niemi et al. 2005).

Statistical analysis

Measurements from the same subject before and after atorvastatin treatment were compared using Wilcoxon signed-rank test. Data were expressed as mean \pm SD. All the data were analyzed with SPSS 17.0 (SPSS, Chicago, IL). The differences were considered statistically significant when $p < 0.05$.

Results

Effect of GBE on pharmacokinetics of atorvastatin

The main pharmacokinetic parameters of atorvastatin (before and after GBE treatment) are shown in Table 1 and Figure 1. After 14 days of treatment by GBE, the value of AUC_{0-48} and the $AUC_{0-\infty}$ substantially decreased by 14.27% ($p = 0.005$) and 10.00% ($p = 0.03$); C_{\max} also significantly decreased by 28.93% ($p = 0.002$); Vd/F and CL/F

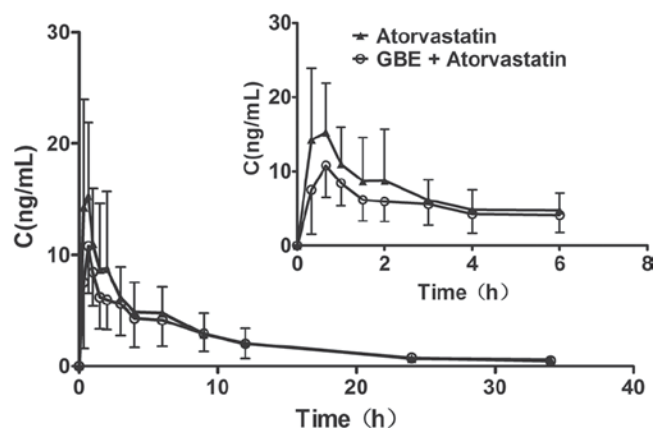


Figure 1. The plasma concentration-time curve of atorvastatin before and after *G. biloba* extract treatment. Data are expressed as mean \pm SD ($n = 16$).

Table 1. Pharmacokinetic parameters of atorvastatin in 16 healthy subjects after a single oral dose of 40 mg atorvastatin with and without *G. biloba* extract.

Variable	Atorvastatin	GBE + Atorvastatin	<i>p</i>
AUC_{0-48} ($\mu\text{g}/\text{L}\cdot\text{h}$)	80.73 \pm 41.24	68.68 \pm 34.02	0.005
$AUC_{0-\infty}$ ($\mu\text{g}/\text{L}\cdot\text{h}$)	87.48 \pm 41.88	76.71 \pm 32.13	0.030
C_{\max} ($\mu\text{g}/\text{L}$)	20.22 \pm 6.61	13.13 \pm 4.54	0.002
t_{\max} (h)	1.02 \pm 1.44	0.71 \pm 0.46	0.754
$t_{1/2}$ (h)	8.12 \pm 3.47	8.71 \pm 3.11	0.352
Vd/F (L)	6318.35 \pm 3745.61	7782.28 \pm 4620.78	0.017
CL/F (L/h)	528.75 \pm 172.41	597.18 \pm 219.50	0.044

GBE, *G. biloba* extract.

significantly increased by 31.95% ($p = 0.017$) and 6.48% ($p = 0.044$); GBE treatment did not significantly alter $t_{1/2}$ and t_{\max} of atorvastatin. As shown in Figure 2, no significant difference in pharmacokinetic parameters was observed for atorvastatin metabolites (2-hydroxyatorvastatin acid, 4-hydroxyatorvastatin acid, atorvastatin lactone, 2-hydroxyatorvastatin lactone, 4-hydroxyatorvastatin lactone) after 14 days of treatment by GBE.

Effect of GBE on atorvastatin efficacy

To further determine whether GBE changes the efficacy of atorvastatin, we determined the plasma cholesterol and noncholesterol sterols concentrations. As shown in Table 2 and Figure 3, GBE did not significantly change the ratio of lathosterol to cholesterol or sitosterol to cholesterol after 14 days of treatment in plasma. On the other hand, after GBE administration, the maximum decrease percentage of lathosterol/cholesterol (at 24 h) changed from 48.6 ± 9.1 to $54.3 \pm 12.7\%$ (Table 2, Figure 3). Although this difference was not significant ($p = 0.055$), there was a trend of additional decrease.

Discussion

GBE is a widely-used and effective memory-improving drug in the treatment of Alzheimer's disease. Statins are

effective for hyperlipidemia treatment. In some patients with nervous system disorder, such as Alzheimer's disease, loss of memory and abnormalities of serum lipid often occur at the same time. Therefore, GBE and statins are frequently used simultaneously in those patients. However, their potential interaction has never been studied before. To gain first-hand information, we designed and carried out this study.

For the first time, we investigated the effects of GBE on the pharmacokinetics and cholesterol-lowering efficacy of atorvastatin in Chinese healthy volunteers. Our data

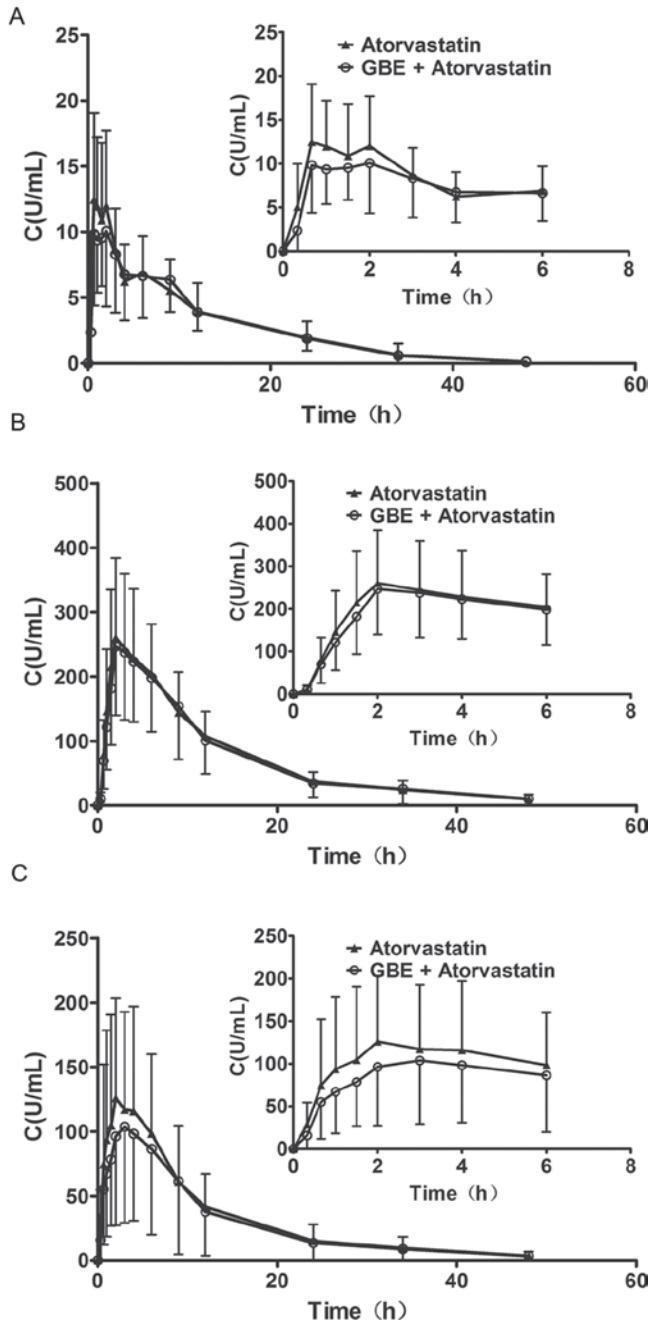


Figure 2. Mean plasma concentrations (\pm SD) of (A) 2-hydroxyatorvastatin acid and 4-hydroxyatorvastatin acid, (B) atorvastatin lactone, (C) 2-hydroxyatorvastatin lactone and 4-hydroxyatorvastatin lactone in 16 healthy volunteers after a single oral dose of 40 mg atorvastatin with and without *G. biloba* extract.

showed that GBE slightly altered AUC, C_{max} , Vd/F and CL/F of atorvastatin.

Atorvastatin is administered as the calcium salt of the active hydroxyl acid form and undergoes marked first-pass metabolism, both in the intestine and in the liver, resulting in an oral bioavailability of \sim 12% (Neuvonen et al. 2006). Atorvastatin and its metabolites are biotransformed mainly by CYP3A4 to form 2-hydroxyatorvastatin and 4-hydroxyatorvastatin (Lennernas 2003). These metabolites are active in the acid form, but inactive in the

Table 2. Characteristics of non-cholesterol sterols to cholesterol ratios in 16 healthy subjects after a single oral dose of 40 mg atorvastatin with and without *G. biloba* extract.

Variable	Atorvastatin	GBE + Atorvastatin	<i>p</i>
Mean % change			
Lathosterol/cholesterol	-32.98 ± 7.65	-36.46 ± 8.99	0.198
Sitosterol/cholesterol	-5.70 ± 24.01	-6.0516 ± 14.96	0.322
Maximum % decrease			
Lathosterol/cholesterol	-48.63 ± 9.14	-54.29 ± 12.73	0.055
Sitosterol/cholesterol	-16.45 ± 23.28	-18.75 ± 23.85	0.743

GBE, *G. biloba* extract.

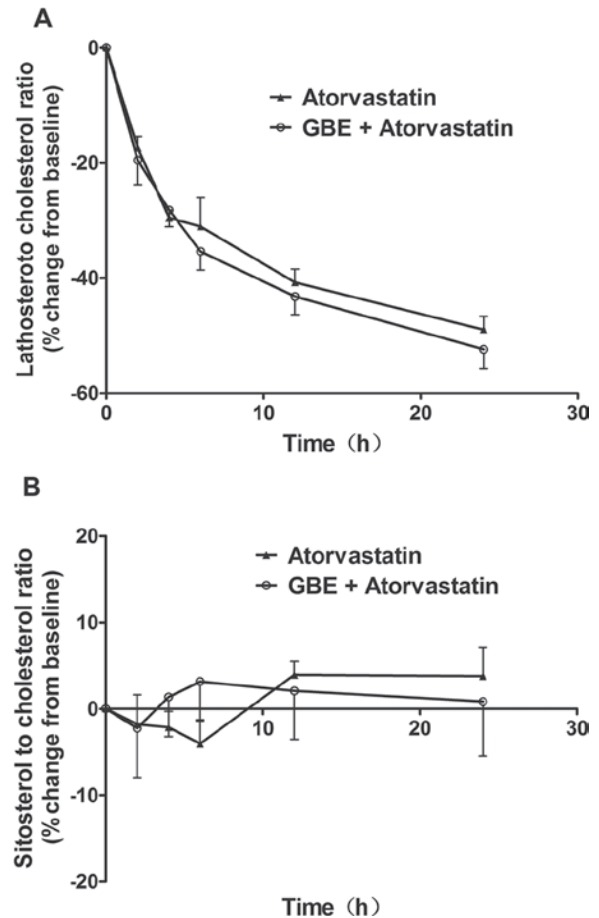


Figure 3. Mean (\pm SD) percent changes from baseline in the plasma (A) lathosterol to cholesterol concentration ratio, (B) sitosterol to cholesterol concentration ratio after a single dose of 40 mg atorvastatin in 16 healthy volunteers with and without *G. biloba* extract.

lipophilic lactone form. Robertson *et al* showed that GBE induced CYP3A4 metabolism and decreased midazolam concentrations (Robertson *et al.* 2008). However, several other studies found that GBE did not affect CYP3A4 activity, for example, GBE did not affect pharmacokinetics of nifedipine, midazolam, donepezil and alprazolam, which are CYP3A4 substrates (Gurley *et al.* 2002; Markowitz *et al.* 2003; Yasui-Furukori *et al.* 2004; Yoshioka *et al.* 2004; Gurley *et al.* 2005). In addition, studies also found that GBE did not significantly affect the pharmacokinetics of warfarin, flurbiprofen, bupropion and diazepam (Jiang *et al.* 2005; Greenblatt *et al.* 2006; Lei *et al.* 2009; Zuo *et al.* 2010). Our results showed that 2-hydroxyatorvastatin and 4-hydroxyatorvastatin plasma concentration did not significantly change after GBE treatment. So we propose that GBE may have little effect on CYP3A4 *in vivo*. Another two enzymes mediating atorvastatin biotransformation are UDP-glucuronosyltransferase1A1 and UGT1A3, which mediate interconversion from the acid to the lactone form of atorvastatin (Riedmaier *et al.* 2010). However, our results showed that the lactone form of atorvastatin did not change significantly after GBE treatment, either. Therefore GBE may also have no effect on UGTs.

It is well known that the genetic polymorphism of OATP1B1 (521T>C, Val174Ala; rs4149056) is strongly associated with statins uptake. The 521CC genotype has been shown to elevate plasma concentrations of atorvastatin, rosuvastatin, simvastatin acid, pitavastatin and pravastatin (Niemi *et al.* 2006; Pasanen *et al.* 2006; Ieri *et al.* 2007; Pasanen *et al.* 2007), and increase risk of statin-induced myopathy (Link *et al.* 2008). To exclude the influence of 521T>C genotype, we analyzed the genotype of OATP1B1 in 17 healthy volunteers. The result showed that 16 subjects are 521TT and one is 521TC. To keep the OATP1B1 genotype consistency, we just involved 16 subjects with 521TT genotype.

Atorvastatin was taken up into hepatic cells mainly by OATP1B1 transporter. P-gp and ABCG2 limit the intestinal absorption and mediates the excretion of atorvastatin into bile (Keskitalo *et al.* 2008; Keskitalo *et al.* 2009). Therefore, lower plasma concentration of atorvastatin is associated with the activity of OATP1B1, P-gp and ABCG2. GBE slightly increased the maximum decrease percentage of lathosterol/cholesterol in this study, which suggests that more atorvastatin might be transported into liver (Table 2). So OATP1B1 transporter activity may be improved by GBE induction. However, further investigations are needed to confirm this conclusion.

Statins decreased plasma concentrations of total and LDL-cholesterol primarily by inhibiting HMG-CoA reductase, which is the rate-limiting enzyme of cholesterol synthesis. Lathosterol can be used as a plasma marker to predict cholesterol-lowering efficacy of atorvastatin. Our data showed that GBE did not change plasma concentration of noncholesterol sterols/cholesterol ratio, indicating that GBE had no effect on atorvastatin efficacy. The study showed that GBE further slightly reduced the maximum

lathosterol/cholesterol concentration ratio after atorvastatin administration. The maximum decrease percentage of lathosterol/cholesterol increased 13.22%. However, these changes were not statistically significant. Thus, the results indicated that GBE did not influence atorvastatin efficacy during this short-term treatment.

In summary, our study indicated that GBE slightly decreased the plasma atorvastatin concentrations, but did not affect atorvastatin cholesterol-lowering efficacy. Thus, GBE can be taken by patients receiving atorvastatin with no clinically significant drug interaction.

Acknowledgment

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Declaration of interest

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