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# Pretreatment with *Ginkgo biloba* extract weakens the hypnosis action of phenobarbital and its plasma concentration in rats

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## Abstract

In a previous study, we found that orally administered *Ginkgo biloba* extract (GBE) induced hepatic cytochrome P450 (CYP) in rats, especially the CYP2B type. This fact suggested that GBE influenced the availability and safety of drugs that were metabolized via CYP2B type enzymes. To confirm this possibility, in this study we examined the effect of feeding a 0.1, 0.5 and 1.0% GBE diet for 2 weeks on the pharmacokinetics and pharmacological action of phenobarbital, which is known to be metabolized by CYP2B in Wistar rats. The feeding of GBE markedly shortened the sleeping time in rats. Furthermore, the maximal phenobarbital plasma concentration ($C_{max}$) and the 24-h area under the curve ($AUC_{0-24}$) were decreased in rats fed GBE. These findings indicate that GBE reduces the therapeutic potency of phenobarbital via enhancement of cytochrome P450 expression, and raises the possibility that GBE and drug interactions may occur clinically.

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## Introduction

*Ginkgo biloba* extract (GBE) comes from a tree that is considered to be a living fossil. This tree is the only remaining representative of its phylum and contains chemical substances not found in any other living specimens. GBE's clinical use encompasses a broad spectrum of pathologies that include peripheral arterial disorders, cardiovascular and neuronal dysfunction and resolution of ischaemia injuries (Clostre 2001; McKenna et al 2001; Mahady 2002). GBE is a popular herbal medicine and is widely and freely used as a dietary supplement without any restrictions in the USA and Japan. However, in European countries, GBE is clinically used for cerebral insufficiency, dementia, intermittent claudication and equilibrium disorders and is designated as EGb 761 (Kleijnen & Knipschild 1992). We have reported that GBE also attenuates the development of hypertension in the deoxycorticosterone acetate (DOCA)-salt hypertensive rat (Umegaki et al 2000). Furthermore, Kubota et al (2001) has shown that GBE potentiates the endothelium-dependent relaxing response by acetylcholine in spontaneously hypertensive rats, but not in Wistar Kyoto rats. This study also suggested that GBE feeding accelerates the increase in intracellular calcium ion levels in endothelial cells. In addition, it has been reported that GBE prevents ischaemia-induced oxidation (Haramaki et al 1994; Koc et al 1995; Pietri et al 1997), produces vasodilatation via nitric oxide (NO) synthesis (Delaflotte et al 1984; Chen et al 1997) and antagonizes the action of platelet-activating factor (Spinnewyn et al 1987). Such reports concerning the pharmacological actions of GBE have been accumulating increasingly. With regard to safety, in some trials that reviewed the adverse event profile of GBE, it was found that GBE was no different to placebo (Le Bars & Kastelan 2000; Birks et al 2002). Thus the data presented so far indicate that GBE use is safe. However, we have reported that a one-month course of oral GBE in rats resulted in increased expression of cytochrome P450 (CYP)2B1/2 and CYP3A types (Shinozuka et al 2002; Umegaki et al 2002). In Japan, elderly people, who have a tendency to take various kinds of medications, are particularly found to use GBE.

Since any effect of GBE would only be revealed after one month of continuous intake (Ernst 2002), simultaneous use of drugs and GBE is thus very likely to occur. The goal of our study is to clarify whether the intake of GBE influences the hypnosis action and the plasma concentration of phenobarbital, a compound that is metabolized by CYP2B1/2 in rats. These findings would provide important information for any patient who commonly ingests GBE.

## Materials and Methods

### Materials

The powder form of GBE, containing 24.2% flavonoids and 9.4% terpenes, was kindly donated by Tama Biochemical Co. Ltd (Tokyo, Japan). Its composition was similar to that of EGb 761 used in European countries. Phenobarbital elixir ($4\,mg\,mL^{-1}$) was purchased from Sankyo Co. Ltd (Tokyo, Japan). Cyclobarbital and sodium pentobarbital were obtained from Tokyo Kasei Kogyo Co. Ltd (Tokyo, Japan). The other reagents were from Wako Pure Chemical Ltd (Osaka, Japan).

### Animals

Male Wistar rats used in the study were cared for in accordance with the procedures outlined in the Guidelines for Animal Experimentation of Mukogawa Women's University, which was compiled from the Guidelines for Animal Experimentation of the Japanese Association for Laboratory Animal Sciences. Rats (SLC, Hamamatsu, Japan; 7 weeks of age) were divided into four groups of four rats each: rats treated without GBE (control group); rats treated with 0.1% GBE (0.1% GBE group); rats treated with 0.5% GBE (0.5% GBE group); and rats treated with 1.0% GBE (1.0% GBE group). These four groups (4 rats/group) were prepared for each of the three experiments described below.

GBE was added to the commercial rodent diet (CE-2; CLEA Japan Inc., Tokyo, Japan) and was given to each of the GBE rats groups. The rats had free access to drinking water. Each group of rats was fed a control diet (CE-2 without GBE) for 7 days and then fed the respective diets for 2 weeks. The liver weight (liver weight/100 g body weight) of feeding rats diets containing 0.5% GBE for 1, 2 and 4 weeks were 4.65, 5.09 and 5.28, respectively. There was no significant difference between the liver weight ratio of rats fed GBE for 2 and 4 weeks.

### Effect of GBE on the liver weight, CYP content and transaminase activity

After 2 weeks feeding, rats were anaesthetized with sodium pentobarbital ($50\,mg\,kg^{-1}$, i.p.). Blood was collected from their abdominal aorta and the liver was rapidly removed, washed in ice-cold saline and weighed. Protein concentration was determined using the bicinchoninic acid (BCA) protein assay kit (Pierce, Rockford, IL). CYP content was measured using a previously described method (Umegaki et al 1995). Plasma transaminases, GOT and GPT, were measured using diagnostic kits from Wako Pure Chemical Industries (Osaka, Japan).

### Effect of GBE on the hypnosis action induced by phenobarbital

Phenobarbital elixir ($90\,mg\,kg^{-1}$) was orally administered using a stomach sonde. The onset of sleep (time from oral administration to loss of righting reflex) for the control and GBE groups and the duration of sleep (the time from loss to recovery of righting reflex) were measured as the sleeping time.

### Effect of GBE on the plasma phenobarbital concentration

For the determination of plasma phenobarbital after the administration, blood samples were taken from the cannula inserted and fixed in the left jugular vein of the rats. Plasma samples were obtained after centrifugation for 10 min at 8000 *g*. A part of the plasma was added to the same volume of acetonitrile that was used with cyclobarbital as the internal standard (IS), and the mixture was centrifuged for 20 min at 8000 *g*. The supernatant solution was filtered through a 0.45-$\mu$m membrane filter and subjected to HPLC. HPLC analysis of phenobarbital was performed on an LC-10ADVP pump (Shimadzu, Kyoto, Japan) with an SPD-6A variable-wavelength ultraviolet detector (Shimadzu) operating at 210 nm. An AS-8020 autosampler (Tosoh, Tokyo, Japan) was used with a Cosmosil $5C_{18}$ column ($150 \times 4.6$ mm, i.d.) (Nakalai Tesque, Tokyo, Japan) and a mobile phase of acetonitrile–water (20:80, v/v) was delivered at a flow-rate of $1.0\,mL\,min^{-1}$. All separations were carried out at 40 °C using a CA-202 column oven (Flom, Tokyo, Japan). The retention times for phenobarbital and the IS were 9.9 and 14.0 min, respectively. The peak areas and final concentrations of phenobarbital were calculated by use of a CLASS-LC10 (Shimadzu). The reproducibility of phenobarbital ($10\,\mu g\,mL^{-1}$, $n = 5$) in plasma was 0.07%. The detection limit of phenobarbital (signal-to-noise ratio of 3) in plasma was 0.5 ng.

### Pharmacokinetic analysis

The maximum plasma concentration ($C_{max}$) and the time to reach the $C_{max}$ ($T_{max}$) after oral administration were determined directly from the measurement values. The area under the plasma concentration–time curve (AUC) was calculated by the trapezoidal method using plasma concentration data.

### Statistics

All values are reported as the mean ± s.e.m. A statistical analysis was performed by Kruskal–Wallis non-parametric analysis of variance. A probability of less than

**Table 1** Body weight and liver weight of rats fed either a control diet or GBE diet (0.1, 0.5, 1.0% GBE) for 2 weeks.

| | Control | 0.1% GBE | 0.5% GBE | 1.0% GBE | Kruskal–Wallis test |
|---|---|---|---|---|---|
| Body weight (g) | 208.5 ± 3.6 | 205.2 ± 2.8 | 200.6 ± 2.0 | 208.7 ± 4.1 | |
| Liver weight (g/100 g body weight) | 3.77 ± 0.08 | 4.36 ± 0.18 | 5.09 ± 0.16 | 5.23 ± 0.17 | ** |

**$P < 0.01$ vs control. Data are means ± s.e.m. (n = 4).

**Table 2** Sleeping lag and sleeping time after oral administration of phenobarbital in rats fed either a control diet or GBE diet (0.1, 0.5, 1.0% GBE) for 2 weeks.

| | Control | 0.1% GBE | 0.5% GBE | 1.0% GBE | Kruskal–Wallis test |
|---|---|---|---|---|---|
| Sleeping lag (min) | 44.3 ± 1.8 | 87.0 ± 5.1 | 89.3 ± 16.8 | 84.0 ± 17.0 | |
| Sleeping time (min) | 479.0 ± 41.9 | 449.5 ± 61.8 | 168.8 ± 86.9 | 178.3 ± 34.0 | * |

*$P < 0.05$ vs control. Data are means ± s.e.m. (n = 4).

0.05 was considered significant. The statistical analyses were carried out with a computer program (Stat View 5.0; Abacus Concepts, Inc., CA).

## Results

Administration of a GBE diet for 2 weeks did not significantly affect body weight, but significantly increased the ratio of liver-to-body weight in rats fed GBE (Table 1). The intake of water and diet of the rats was not influenced by GBE at all, and there was no change in behaviour. The 1.0% GBE diet increased liver weight 1.38 fold as compared with controls. As there was no significant difference between the ratio of liver-to-body weight for the 0.5% and 1.0% GBE group, 0.5% GBE was deemed to produce a maximal effect on the liver weight. The CYP content in the liver of control rats and the 0.5% GBE rats was 0.46 ± 0.07 (n = 4) and 1.84 ± 0.13 (n = 4) nmol (mg protein)$^{-1}$, respectively. Thus, the 0.5% GBE diet significantly enhanced the CYP content of the liver ($P < 0.01$). The serum transaminases, GOT and GPT, were unaffected by the GBE diet (data not shown). These results are basically the same as data previously reported in a study where 0.5% GBE was administered for four months (Shinozuka et al 2002).

Table 2 shows the effects of a 2-week course of GBE on orally administered phenobarbital (90 mg kg$^{-1}$)-induced sleeping start time and total sleeping time. GBE administration tended to delay the sleeping start time and significantly produced a shortening of the total sleep time caused by phenobarbital. Since there was no significant difference between the sleeping time for the 0.5% and 1.0% GBE groups, 0.5% GBE was deemed as being able to produce a maximal effect on the hypnosis action of phenobarbital.

Figure 1 illustrates the effects of a 2-week course of GBE on the rat plasma phenobarbital concentrations following the oral administration of phenobarbital. GBE significantly depressed the plasma concentration of phenobarbital at 1.0, 4.0 and 8.0 h. The $C_{max}$ of phenobarbital was significantly reduced by GBE, though the time to reach maximum concentration after administration was not changed (Table 3). The $AUC_{0-24}$ (area under the curve from 0 to 24 h after the oral administration) tended to be reduced by GBE, although the differences were not significant (Table 3).

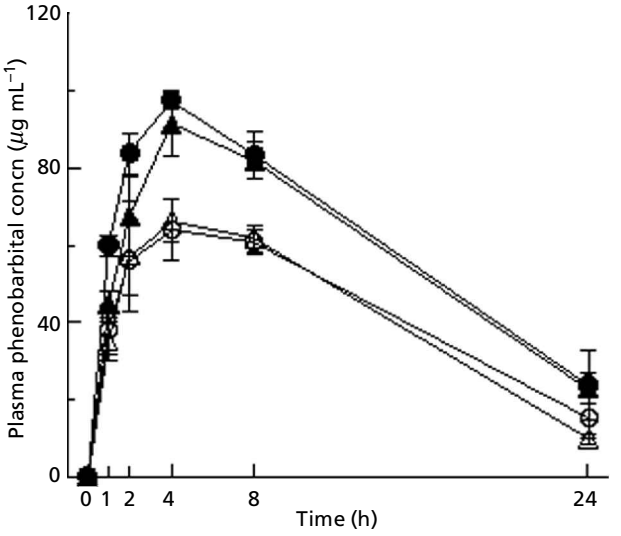


**Figure 1** Plasma concentration of phenobarbital in rats after the administration of phenobarbital to rats fed on either a control diet (●) or on a GBE diet (▲, 0.1%; ○, 0.5%; △, 1.0%) for 2 weeks. Each point indicates means ± s.e.m. (n = 4).

**Table 3** Plasma concentration of phenobarbital after oral administration to rats fed either a control diet or GBE diet (0.1, 0.5, 1.0% GBE) for 2 weeks.

| | Control | 0.1% GBE | 0.5% GBE | 1.0% GBE | Kruskal–Wallis test |
|---|---|---|---|---|---|
| $T_{max}$ (h) | 3.5 ± 0.5 | 4.0 ± 0 | 3.5 ± 0.5 | 4.5 ± 1.3 | |
| $C_{max}$ ($\mu g\,mL^{-1}$) | 99.1 ± 1.7 | 91.4 ± 8.4 | 64.8 ± 7.3 | 70.1 ± 3.3 | * |
| $AUC_{0-24}$ ($\mu g\,h\,mL^{-1}$) | 543.5 ± 76.4 | 533.1 ± 79.0 | 446.4 ± 78.1 | 465.5 ± 32.2 | |

*$P < 0.05$ vs control. Data are means ± s.e.m. (n = 4).

## Discussion

We have previously shown that GBE administration in rats markedly increased the content of CYP and the level of CYP2B mRNA in the rat liver (Shinozuka et al 2002). Furthermore, we also reported that GBE administration increased CYP concentrations and the activity of various CYP enzymes, especially pentoxyresorufin O-dealkylase, in the liver in a time- and dose-dependent manner (Umegaki et al 2002). At the same time, marked induction of CYP2B1/2B2 by GBE administration was confirmed by Western blot analysis. As pentoxyresorufin O-dealkylase is a CYP2B enzyme, the increases in both the activity and mRNA correspond well. These findings indicate that intake of GBE induced the CYP2B type enzyme. Therefore, it can be expected that GBE intake may reduce the efficacy of medications that are substrates for the CYP2B1/2B2 enzymes.

In this study, the daily intake of GBE was approximately $1.3\,g\,kg^{-1}$, based on the rat GBE group that was fed a mix with 0.5% GBE. In Europe, the clinical dose of EGb 761 is 120–360 mg daily (p.o.). The dose of GBE in this study is about 216–650 times that of the dosages currently used in man. Therefore, our findings do not directly relate to the influence of GBE in man. However, we have shown that significant induction of CYP was detected at a dose of $10\,mg\,kg^{-1}$ GBE, and the influence of GBE on CYP was observed in human and rat microsomes (Umegaki et al 2002). Thus, if people consume an excess of GBE as compared with ordinary intake levels, significant induction of CYP enzymes may occur, similar to that shown in this study. It should be especially noted that GBE induces not only CYP2B1/2 but also the CYP3A type (Shinozuka et al 2002), which is an enzyme known to metabolize many compounds in use today. This fact may indicate that interaction between GBE and drugs can occur, resulting in disturbance of therapeutics used for disease treatment by the medical community.

As a clinical example, it was reported that self-medication with St John's wort has led to a drop in plasma levels of ciclosporin, causing tissue rejection in transplant patients (Mai et al 2000; Ruschitzka et al 2000; Barone et al 2001). Indeed, there are many reports that the intake of St John's wort enhances the expression of CYP3A4 in the liver and intestine (Durr et al 2000; Markowitz et al 2000; Roby et al 2000) and stimulates the metabolism of the immunosuppressant drug ciclosporin, resulting in subtherapeutic plasma concentrations. Also, it is well known that flavonoids in grapefruit juice inhibit CYP in human liver microsomes (Buening et al 1981; Bailey et al 1991) and intestine (Bailey et al 1996).

Thus, the probability of the occurrence of adverse interactions caused by GBE in conjunction with synthetic medicines may not be small. Moreover, increases in CYP activity by GBE treatment may accelerate the conversion of environmental chemicals or carcinogens to not only inactive but also active forms, such as benzopyrene or aflatoxin B1 (Qualls et al 1998; Kuilman et al 2000). Therefore, physicians and pharmacists need to pay attention to the possibility of drug interactions with dietary supplements. However, the experimental reports in the field of dietary supplements and drug interactions are quite limited when one looks at the number of dietary supplements currently being sold and used. Further studies that focus on these matters are needed to ensure effective use of GBE and dietary supplements.

### Conclusion

We found that the feeding of GBE for 2 weeks markedly weakened the hypnosis action of phenobarbital and decreased the plasma concentrations of phenobarbital in rats. This finding is consistent with our previous report that GBE induced hepatic cytochrome P450, especially CYP2B1/2, which is the enzyme that metabolizes phenobarbital in rats (Shinozuka et al 2002; Umegaki et al 2002). Some dietary supplements may potentially influence the efficacy of medications in man, and thus require special attention with regard to their use in clinical situations. These results provide important information for using GBE more safely and effectively without drug interaction.

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