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ALTERED ORAL ABSORPTION OF ALCOHOL BY COMBINED AQUEOUS EXTRACTS OF FOUR HERBAL PLANTS IN RATS

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This study examined the effect of combined aqueous extracts (BHR) of Ginko biloba, Mentha arvensis var. piperascens, Citrus unshiu, and Pueraria lobata var. chinensis on oral absorption of alcohol in rats. The rats were pretreated with BHR, placebo solution identical to BHR without the herbal extract, and isotonic saline. Alcohol was administered orally at 1- and 3-g/kg doses and the absorption profiles were compared. After oral administration of 1-g/kg doses, mean area under the curve (AUC) and C_{max} values were significantly reduced in BHR-treated rats (16.1 ± 10.0 and 0.3 ± 0.1 mg/ml, respectively) as compared with saline-treated (37.9 ± 14.4 and 0.7 ± 0.7 mg/ml, respectively) and placebo solution-treated (63.0 ± 46.4 and 0.7 ± 0.4 mg/ml, respectively) rats. Similarly, after administration of 3-g/kg doses, mean AUC and C_{max} values in BHR-treated rats (188.1 ± 119.7 mg min/ml and 1.0 ± 0.4 mg/ml) were significantly reduced over those in saline-treated rats (571.4 ± 512.4 mg min/ml and 1.8 ± 0.9 mg/ml, respectively). The relative oral bioavailability of alcohol calculated as the ratio of AUC_{BHR}/AUC_{Saline} was 42.5% and 32.9% at 1- and 3-g/kg doses, respectively. The reduced serum alcohol levels as well as the reduced AUC and C_{max} after pretreatment with BHR appear to be a result of a reduced systemic absorption not due to an increased metabolic clearance.

Various factors modifying blood alcohol levels have been reported, including carbohydrates (Keegan & Batey, 1993), liquid diets and fructose (Erickson & Byers, 1989), and food (Hahn et al., 1994). Several herbal extracts and their constituents, such as *Salvia miltiorrhiza* (Colombo et al., 1999), angelica barks (Lipkin, 1995), *Panax ginseng* (Lee et al., 1993), bay leaf (*Laurus nobilis*) (Yoshikawa et al., 2000), aloin, a quinone derivative of *Aloe* (Chung et al., 1996), isoflavones from *Pueraria lobata* (Lin & Li, 1998; Xie et al., 1994), and antioxidants from green tea (Luczaj et al., 2004) have been reported to alter blood alcohol levels or exert protective effects against alcohol induced toxicities.

Ginko biloba, *Mentha arvensis* var. *piperascens*, *Citrus unshiu*, and *Pueraria lobata* var. *chinensis* have been used in Chinese folk medicine for the treatment of a number of disorders, such as intermittent claudication, cognitive impairment, cerebral disorders, peripheral circulatory disturbances (Curtis-Prior et al.,

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1999; Oken et al., 1998; Pittler & Ernst, 2000), inflammation-associated tumorigenesis (Murakami et al., 2000), irritable bowel syndrome (Pittler & Ernst, 1998), and alcohol abuse (Keung & Vallee, 1998). This study was conducted to examine the effects of combined aqueous extracts of these medicinal plants after intragastric administration of alcohol (1- or 3-g/kg dose) to rats. Our results showed that the herbal extract significantly reduced serum alcohol levels as well as C_{\max} and AUC as compared with those found in placebo solution- and saline-treated rats.

MATERIALS AND METHODS

Chemicals

Ethyl alcohol was purchased from Carlo Erba Co. (Val de Reuil, France). Alcohol dehydrogenase, anhydrous sodium pyrophosphate, β -NAD lithium salt, ketamine, xylazine, phenylhydrazine, monobasic potassium phosphate, and dibasic potassium phosphate trihydrate were obtained from Sigma Chemical Co. (St. Louis, MO). Acetonitrile and methanol (all high-performance liquid chromatography [HPLC] grades) were purchased from Fisher Scientific Co. (Pittsburgh, PA).

Preparation of BHR and Placebo Solution

Aqueous herbal extracts were prepared from the fructus of *Ginko biloba*, dried aerial parts of *Mentha arvensis* var. *piperascens*, pericarps of *Citrus unshiu*, and dried flowers of *Pueraria lobata* var. *chinensis*. They were cut into small pieces and extracted with distilled water (1:10 w/v) under reflux at 80°C over a 2-h period. The extracts were filtered and concentrated at 60°C under reduced pressure. One gram of the combined and concentrated extract was equivalent to 2.5 g *Ginko biloba*, 2.5 g *Mentha arvensis* var. *piperascens*, 1.75 g *Citrus unshiu*, and 1 g *Pueraria lobata* var. *chinensis*. The composition of the combined aqueous extracts, BHR (100 ml), was as follows: concentrated herbal extract 1 g, taurine 1 g, sugar 9 g, stevioside 50 mg, sodium chloride 40 mg, sodium benzoate 50 mg, citric acid 180 mg, sodium citrate 15 mg, and distilled water. The placebo solution was identical to BHR without herbal extract.

Animals

Male Sprague-Dawley rats (7–9 wk of age, 200–250 g) were purchased from Hanlim Animals Co. (Seoul, Korea) and were kept in plastic rat cages with free access to standard rat diet (Samyang, Seoul, Korea) and water. The rats were maintained in an animal facility at a temperature of $23 \pm 2^\circ\text{C}$ with a 12/12-h light/dark cycle and relative humidity of $50 \pm 10\%$. The rats were anesthetized by intraperitoneal (ip) injection of ketamine and xylazine (90/10 mg/kg) and cannulated with polyethylene (PE) tubing (0.58 mm ID and 0.96 mm OD Natume Co., Tokyo) in the right femoral vein. After surgery, at least 2 d of recovery period was allowed prior to experimentation.

Alcohol Administration Study

The rats were divided into 5 groups ($n = 4-6$). Groups 1-3 were pretreated orally (1 ml each) with BHR, a placebo solution identical to BHR without herbal extract, and saline, respectively. Thirty minutes after pretreatment, alcohol was administered by oral gavages at a dose of 1 g/kg. Groups 4 and 5 ($n = 6$ each) were also pretreated orally with BHR and saline (1 ml each), respectively, and 30 min later, alcohol was administered at a dose of 3 g/kg. Serial venous blood samples (0.2 ml each) were taken at 0, 5, 10, 15, 30, 45, 60, 90, and 120 min. Following administration of a higher dose (3 g/kg), additional samples were taken at 3 and 5 h. Equal volumes of saline were replaced after each sampling. Serum samples were harvested by centrifugation at $1500 \times g$ for 10 min and kept at -20°C until analysis.

HPLC Analysis

Alcohol concentrations in serum samples were determined by a high-performance liquid chromatography (HPLC) method reported previously (Pellegrino et al., 1999). A stock solution was prepared by diluting ethyl alcohol to 100 ml with distilled water (concentration 2 mg/ml). For the construction of standard curves, the stock solution was diluted to 20, 50, 100, 500, 1000, 2000, and 4000 $\mu\text{g/ml}$. To a borosilicate tube (Scientific Glass, Inc., Rockwood, TN) were added 1 ml pyrophosphate (74 mM, pH 9.2, adjusted with hydrochloric acid), 40 μl phenylhydrazine solution (480 mM), 80 μl β -NAD solution (50 mM), and 20 μl alcohol dehydrogenase suspension (30 IU), and the mixture was vortexed for 10 s. A portion (20 μl) of the serum sample was added to the tube, vortexed, and incubated at 30°C for 30 min. At the end of incubation, the solution was centrifuged at $1500 \times g$ for 30 s and a portion (10 μl) was injected onto HPLC.

Chromatographic Conditions

The chromatographic system used in the study was a Gilson HPLC component system consisting of a model 307 pump, a model UV-118 ultraviolet (UV)-visible detector, a model 234 autosampler, a model 506 system interface module, and a model 811C dynamic mixer (Gilson Co., Middleton, WI). Chromatographic separations were achieved using a LiChrospher RP-18 analytical column (Merck, 4.0 mm \times 125 mm, 5 μm) and a guard column (Merck, 4.6 mm \times 10 mm, 5 μm) (Darmstadt, Germany). The mobile phase consisted of KH_2PO_4 (14.7 mM): $\text{K}_2\text{HPO}_4 \cdot 3\text{H}_2\text{O}$ (8.8 mM):acetonitrile (15:45:40, v/v). The mobile phase was filtered (0.26 μm) and degassed by ultrasonication under vacuum before use. The flow rate of the mobile phase was 1.5 ml/min, and the effluent was monitored at a UV detection wavelength of 276 nm. The standard curves were linear over the concentration range of 20-4000 $\mu\text{g/ml}$, with a typical correlation coefficient $r > .9999$. The intra- and interday assay coefficients of variation were 5.1% and 6.4%, determined at alcohol concentrations of 100 and 50 $\mu\text{g/ml}$, respectively.

Data Analysis

Serum alcohol concentration–time data were analyzed by a noncompartmental method using the nonlinear least squares regression program WinNonlin (Scientific Consulting, Inc., Cary, NC). Pharmacokinetic parameter values of the maximum concentration (C_{\max}), time to C_{\max} (t_{\max}), apparent volume of distribution (V/F), oral clearance (Cl/F), area under the curve (AUC), area under the first moment curve (AUMC), mean residence time (MRT), and apparent elimination half-life ($t_{1/2,\lambda_z}$) were determined and expressed as the mean \pm SD. Differences in the pharmacokinetic parameters among groups were tested by one-way analysis of variance (ANOVA) and Student's t -test for the 1- and 3-g/kg doses, respectively. The statistical significance was set at $p < .05$.

RESULTS

Figure 1 shows mean serum alcohol concentration–time profiles after oral administration of alcohol (dose 1 mg/kg) to rats pretreated with BHR, placebo solution, and isotonic saline. Serum levels of alcohol in BHR-pretreated rats were significantly lower at 5, 10, 15, 30, 45, and 60 min compared with those in placebo- and saline-pretreated groups. Serum alcohol levels between placebo- and saline-pretreated groups were not significantly different. Pharmacokinetic parameters of alcohol obtained in three groups of rats are summarized in

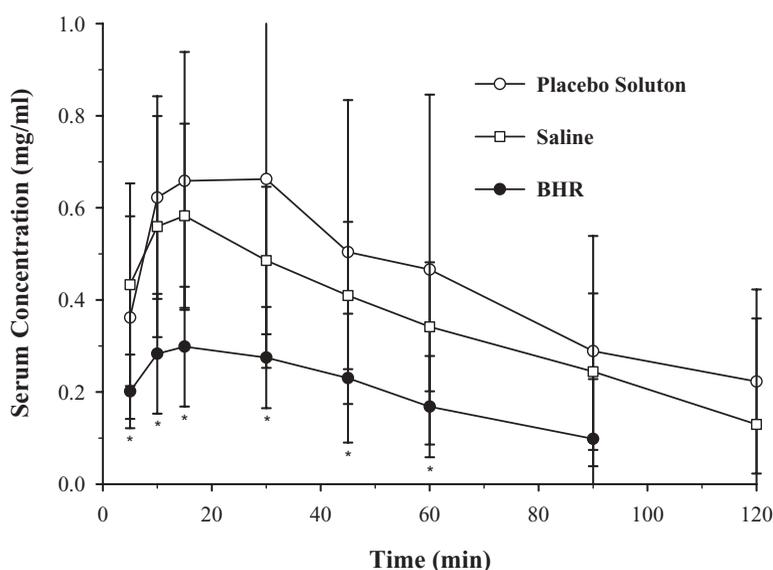


FIGURE 1. Serum alcohol concentration-time curves (mean \pm SE) in rats treated with BHR, saline, or placebo solution after oral administration of alcohol (dose 1 g/kg). Asterisk indicates significant at $p < .05$ versus saline and placebo solution.

TABLE 1. Pharmacokinetic parameters of alcohol obtained after oral administration (dose 1 g/kg) in rats (mean \pm SD)

Parameter	Saline	BHR	Placebo solution
Body weight (g)	223 \pm 16	223 \pm 23	203 \pm 5
t_{\max} (min)	10.0 \pm 3.5	16.0 \pm 8.2	16.3 \pm 9.5
C_{\max} (mg/ml)	0.7 \pm 0.2	0.3 \pm 0.1 ^{a,b}	0.7 \pm 0.4
AUC (mg·min/ml)	37.9 \pm 14.4	16.1 \pm 10.0 ^{a,b}	63.0 \pm 46.4
λ_z (min ⁻¹)	0.040 \pm 0.011	0.063 \pm 0.024 ^{a,b}	0.029 \pm 0.015
$t_{1/2,\lambda_z}$ (min)	18.3 \pm 4.3	12.5 \pm 5.3 ^{a,b}	30.6 \pm 16.2
V_z/F (ml)	156.7 \pm 112.9	293.0 \pm 268.2	152.2 \pm 93.9
Cl/F (ml/min)	5.6 \pm 2.9	16.7 \pm 13.3	4.8 \pm 5.0
AUMC (mg·min ² /ml)	1597 \pm 734	576 \pm 483 ^{a,b}	4472 \pm 4088
MRT (min)	40.8 \pm 4.8	32.1 \pm 7.8 ^{a,b}	60.2 \pm 22.3 ^c

^a Significant at $p < .05$, BHR vs. saline.

^b Significant at $p < .05$, BHR vs. placebo solution.

^c Significant at $p < .05$, saline vs. placebo solution.

Table 1. The mean C_{\max} and AUC in BHR-treated rats (0.3 ± 0.1 mg/ml and 16.1 ± 10.0 mg·min/ml, respectively) were significantly lower than in saline-treated (0.7 ± 0.7 mg/ml and 37.9 ± 14.4 , respectively) and placebo solution-treated (0.7 ± 0.4 mg/ml and 63.0 ± 46.4 , respectively) rats. The mean V/F and Cl/F values were similar between placebo (156.7 ± 112.9 ml and 5.6 ± 2.9 ml/min, respectively) and saline-treated (152.2 ± 93.9 ml and 4.8 ± 5.0 ml/min, respectively) groups but were higher with BHR (293.0 ± 268.2 ml and 16.7 ± 13.3 ml/min, respectively). The apparent elimination half-life ($t_{1/2,\lambda_z}$) was significantly reduced in BHR-treated (12.5 ± 5.3 min) compared with placebo (30.6 ± 16.2 min) and saline-treated (18.3 ± 4.3 min) rats.

Figure 2 shows the mean serum alcohol concentration-time curves after oral administration of alcohol (dose 3 mg/kg) to rats pretreated with BHR or saline. Serum levels of alcohol in BHR-treated rats were lower, with the differences being significant at 10 and 15 min. Obtained pharmacokinetic parameters are summarized in Table 2. The mean C_{\max} and AUC in BHR-treated (1 ± 0.4 mg/ml and 188.1 ± 119.7 mg·min/ml, respectively) were lower than those in saline-treated rats (1.8 ± 0.9 mg/ml and 571.4 ± 512.4 mg·min/ml, respectively). The mean V/F was significantly increased in BHR-treated versus saline-treated rats (310.1 ± 119.8 ml vs. 178.7 ± 82.9 ml), but these values were similar to the corresponding values found after administration of the 1-g/kg dose. The Cl/F in the BHR group (3.7 ± 2.4 ml/min) was higher than in the saline group (2.2 ± 2.2 ml/min). The apparent elimination half-life ($t_{1/2,\lambda_z}$) was not significantly affected in the BHR group (69.6 ± 30.1 min) versus saline (139.9 ± 120.7 min).

DISCUSSION

The relative bioavailability of alcohol in BHR-treated rats calculated as the ratio of $AUC_{\text{BHR}}/AUC_{\text{Saline}}$ was 42.5 and 32.9% at 1- and 3-g/kg doses, respectively.

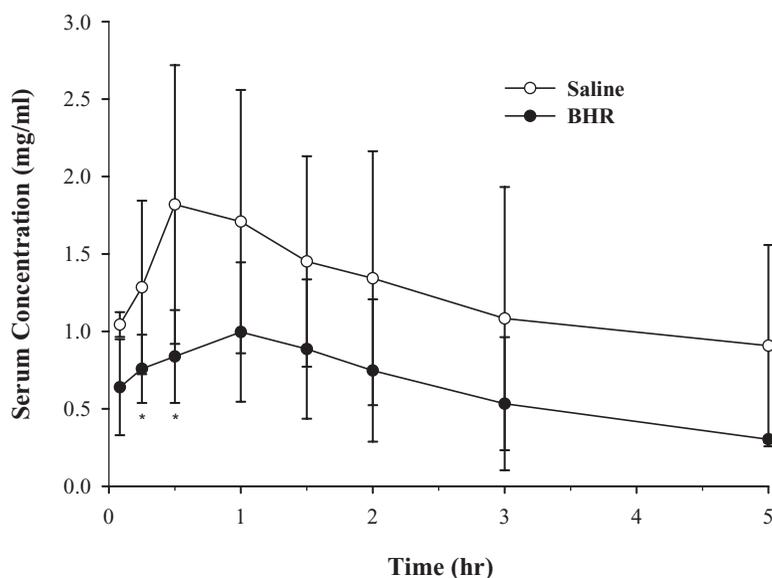


FIGURE 2. Serum alcohol concentration-time curves (mean \pm SE) in rats treated with BHR or saline after oral administration of alcohol (dose 3 g/kg). Asterisk indicates significant at $p < .05$ versus saline.

TABLE 2. Pharmacokinetic parameters of alcohol obtained after oral administration (dose 3 g/kg) in rats (mean \pm SD)

Parameter	Saline	BHR
Body weight (g)	202 \pm 4	205 \pm 8
t_{\max} (min)	45.0 \pm 25.1	50.0 \pm 29.5
C_{\max} (mg/ml)	1.8 \pm 0.9	1.0 \pm 0.4 ^a
AUC (mg·min/ml)	571.4 \pm 512.4	188.1 \pm 119.7
λ_z (min ⁻¹)	0.015 \pm 0.020	0.012 \pm 0.005
$t_{1/2, \lambda_z}$ (min)	139.9 \pm 120.7	69.6 \pm 30.1
V_z/F (ml)	178.7 \pm 82.9	310.1 \pm 119.8 ^a
Cl/F (ml/min)	2.2 \pm 2.2	3.7 \pm 2.4
AUMC (mg·min ² /ml)	197,554 \pm 262,844	26,970 \pm 21,471
MRT (min)	225.9 \pm 161.8	127.3 \pm 41.2

^a Significant at $p < .05$, BHR vs. saline.

Serum alcohol levels and pharmacokinetic parameters for the placebo and saline groups were not significantly different from each other. The placebo used in this study was identical to BHR except for the herbal extract, and therefore the reduced serum alcohol levels in BHR-treated rats do not appear to be produced by taurine and stevioside present in BHR or an increased calorie intake from sugar.

Pretreatment with BHR significantly altered the serum alcohol levels, C_{\max} , V/F , Cl/F , and AUC compared with saline-treated rats at both 1- and 3-g/kg doses. A threefold increase in administered dose of alcohol resulted in approximately proportional increases in C_{\max} in BHR- and saline-treated rats (2.6- and 3.3-fold increases, respectively). The apparent volume of distribution (V/F) was unaltered as a function of dose in both saline (156.7 vs. 178.7 ml) and BHR (293.0 vs. 310.1 ml) groups, indicating that the volume of distribution of alcohol was not altered over the dose range studied. Alcohol is known to distribute primarily to body fluids (Lands, 1998; Tzamaloukas et al., 1985). The increased V/F in the BHR group was a result of a reduced bioavailability. On the other hand, a threefold increase in administered dose of alcohol resulted in a nonproportional increase in AUC in both the BHR and saline groups (15.1- and 11.2-fold, respectively). In addition, Cl/F was reduced and $t_{1/2,\lambda z}$ was elevated as the dose was increased in both groups of rats. These findings are consistent with the alcohol elimination characteristics that follow parallel first-order and Michaelis–Menten kinetics, with the alcohol dehydrogenase-dependent pathway readily saturable (Fujimiya et al., 1989). According to the allometric scaling for the volume of distribution of alcohol in mammals [$V = 0.762W^{0.932}$; V is the volume of distribution (L); W is the body weight (kg)] (Matsumoto et al., 1999), predicted values in the saline-treated rats (107.3–117.6 ml) are lower than observed V/F values (152.2–178.7 ml). Assuming a volume of distribution of 550 ml/kg body weight (Matsumoto et al., 1999), the mean disappearance rate of alcohol at a dose of 1 g/kg was calculated as 190, 270, and 282 mg/hr/kg in BHR-, placebo solution-, and saline-treated rats, respectively. In addition, at a 3-g/kg dose, the alcohol disappearance rate was 263 and 240 mg/h/kg in the BHR and saline groups, respectively. Therefore, it is reasonable to conclude that the BHR treatment did not increase the disappearance rate of alcohol.

In conclusion, the BHR treatment resulted in decreased blood alcohol levels and reduced AUC and C_{\max} in rats following administration of alcohol at 1- and 3-g/kg doses. These alterations may be a result of a reduced systemic absorption rather than increased elimination. Further study is warranted to identify the active components of the herbal extracts in BHR responsible for the reduced absorption of alcohol.

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