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Platycodin D Shows Anti-inebriation Effects in Alcohol-loaded Mice

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Abstract

Platycodin Dis the main active saponin in *Platycodon grandiflorum*. The purpose of this study was to investigate the effects of platycodin D on acute alcohol intoxication as well as the possible mechanisms of alcohol metabolism. Alcohol-loaded mice were used as the experimental model to evaluate the recovery period of the righting reflex, the serum concentrations of alcohol and acetaldehyde, the activity and gene expression of alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH), the levels of malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT) and the glutathione (GSH) in liver. The results showed that alcohol-loaded mice treated with platycodin D exhibited latency in the alcohol-induced loss of the righting reflex, a shorter recovery period of the righting reflex, and lower concentrations of alcohol and acetaldehyde in serum. In addition, the activity and gene expression of ADH and ALDH in the liver were significantly increased ($p<0.05$). Platycodin D was also found to decrease the MDA level and increase the SOD, CAT and GSH levels in liver ($p<0.05$). These results suggest that the anti-inebriation effects of platycodin D may involve accelerating alcohol metabolism and enhancing hepatic anti-oxidative functions.

Keywords: Platycodin D; Anti-inebriation; ADH; ALDH; MDA

Introduction

In many countries, light-to-moderate alcohol consumption is considered an integral part of the diet, and drinking alcoholic beverages is common at social gatherings [1]. However, excessive drinking of alcohol will cause serious health problems, such as alcoholic liver and stomach disease [2]. Furthermore, alcohol abuse is also associated with societal problems, such as social violence, traffic accidents and economic burden [3-5].

Approximately 80-90% of the alcohol absorbed is metabolized to acetaldehyde and acetate via hepatic oxidation by alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH), respectively [6,7]. The high levels of ADH generated during alcohol metabolism are the primary defense against alcohol, detoxifying alcohol in the liver and stomach [8]. In addition, acetaldehyde is responsible for "alcohol hangover", which can cause vasodilation, flushing of the face, nausea, and headache; thus, it is more toxic to the body than alcohol [9,10]. Therefore, complications of alcohol intake could be resolved by effectively decreasing the serum alcohol and acetaldehyde concentrations.

Several herbal medicines, such as asparagus, ginseng root, and green tea, have been shown alleviate hangover via stimulation of ADH and ALDH [11-13]. Platycodin D is the main active saponin in *P. grandiflorum*, and currently, there is much interest in Platycodin D because of its physiological functions, including its cholesterol-lowering activity [14], prostaglandin E2 production inhibitory activity [15], antioxidant activity [16], anti-atherosclerotic activity [17], and liver protective activity [18]. However, previous research suggests a relationship between platycodin D and anti-inebriation, which has not been reported. Thus, the objective of this study was to evaluate the effects of platycodin D on the following in alcohol-loaded mice: (1) the recovery period of the righting reflex; (2) the alcohol and acetaldehyde concentrations in serum from mice 0.5, 1.0, and 2.0 h after administration of 52% alcohol; (3) the activity and gene expression of alcohol metabolizing enzymes (ADH, ALDH); (4) the levels of malondialdehyde (MDA) and the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) in liver.

Materials and methods

Materials

Alcohol (52%, wt./vol) was purchased from the Jinliufu brewery (Beijing, China). Authentic standards of butyl aldehyde-2,4-dinitrophenylhydrazine (BUH-DNPH) and andacetaldehyde-2,4-dinitrophenylhydrazine (ACH-DNPH)were purchased from Sigma-Aldrich (Shanghai, China). Platycodin Dwas purchased from Chengdu Best Reagent (Chengdu, China). The acetonitrile, isopropanol and methanol used were chromatographic grade and purchased from Fisher Chemicals (Shanghai, China). All other chemicals used were of analytical grade and were purchased from Beijing Chemical Reagent (Beijing, China).

Preparation ofplatycodin D

Platycodin D from the root of Platycodon grandiflorum was extracted and purified according to a previous reported method with modification [19]. The constituent of this extraction process was determined using high performance liquid chromatography (HPLC) (Shimazu, Japan). An Alltima C18 column (250 mm × 4.6 mm, 5 μm) (Agilent, USA) was used at room temperature in this analysis. The mobile phase consisted of acetonitrile and water. The elution profile was as follows: 0-28 min, isocratic at 25% (v/v) B; 28-38 min, linear

gradient from 25 to 33% (v/v) B; 38-42 min, linear gradient from 33 to 90% (v/v) B; 42-50 min, isocratic on 25% (v/v) B; 50-52 min, linear gradient from 90 to 25% (v/v) B; and 52-60 min, isocratic on 25% (v/v) B; the flow rate was set at 1.0 mL/min; and the elute after the column was sent to an evaporative light scattering detector (ELSD). The ELSD conditions were optimized to achieve maximum sensitivity, the temperature of the drift tube was set at 103.8°C, the nebulizing gas flow rate was set at 2.8 L/min, and the gain was set at 1.

Identification and quantification of platycodin D in samples were performed by comparison with the chromatographic retention times and areas of external standard. A calibration curve for a platycodin D standard was constructed using an authentic standard. On the basis of peak areas, the purity of platycodin D was 95.73% (Figure 1).

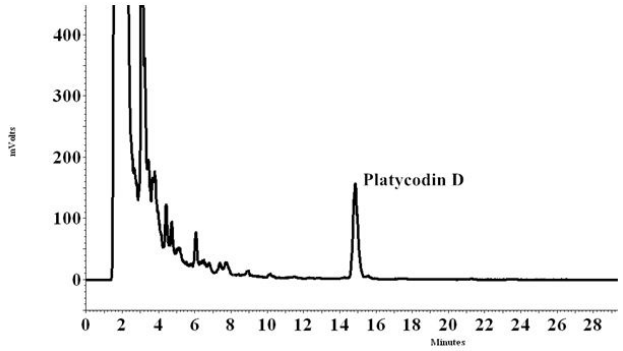

Figure 1: HPLC Chromatograms of platycodin D isolated from the root of *P. grandiflorum*.

Animals

Male ICR mice (25-30 g) were obtained from the Department of Laboratory Animals at Peking University (Beijing, China). After acclimation for 3 days in an environmentally controlled room at 20 ± 2°C with a 12 h light-dark cycle, the mouse diet was administered according to the general quality standard for formula feeding of laboratory animals in China. The experiment was performed in compliance with the principles of the institute of laboratory animal resources and approved by the Peking University committee on animal care and use.

Righting reflex evaluation

Mice were randomly assigned to three experimental groups (n=12); mice in each group were orally administered 52% alcohol (16 mL/kg body weight). One-half hour after alcohol administration, the control group (CG) received saline (20 mL/kg body weight), the low dose group (LDG) received platycodin D (0.5 mg/mL) at 20 mL/kg body weight, and the high dose group (HDG) received platycodin D (1.0 mg/mL) at 20 mL/kg body weight. Animals were deprived of food and water during the experiments. The period of loss of the righting reflex and the latency period for recovery of the righting reflex was recorded Zhang et al. [20]. The rate of intoxication (%) was calculated as (the number of inebriated mice/the number of inebriated and sober mice) × 100.

Experiment for pharmacokinetic study

Mice were randomly assigned to four experimental groups (n=12), and the drug administration protocols of three groups (CG, LDG and HDG) were identical to those used for the righting reflex evaluation, mice in another group orally administered saline twice (16 mL/kg and 20 mL/kg body weight) was used as the normal group (NG). Blood samples from the infra-orbital venous plexus were collected at 0.5, 1.0, 2.0 h after alcohol administration. The serum was collected by centrifugation at 10,000 rpm for 3 min at 4°C and stored at -80°C until further analysis. Liver tissue from each mouse was collected at 2.0 h after alcohol administration. The tissue samples were snap-frozen in liquid nitrogen and stored at -80°C until further experimentation.

Alcohol and acetaldehyde concentrations in serum

The alcohol concentration was determined by gas chromatography (GC) according to Li et al. [21] with some modifications. One-hundred microliters of perchloric acid was added to 0.2 mL of serum in a 1.5 mL tube, and isopropanol was adjusted to a final concentration of 100 ppm as an internal standard. The mixture was centrifuged at 10000 rpm for 5 min after briefly vortexing, and the clear supernatant was transferred to a clean tube for GC analyses. GC analyses were performed on a Model 6890A GC (Agilent, California, USA) coupled with a flame ionization detector (FID). The capillary column (HP-innowax; 30 m × 0.32 mm × 0.5 μm) was used in this analysis. The injector port temperature was 200°C, and the initial oven temperature of the GC was 60°C. After maintaining the oven at that temperature for 2 min, the oven temperature was increased at a rate of 10°C/min to reach a final temperature of 200°C. The mobile phase was nitrogen and the constant flow rate was 1.0 mL/min.

The acetaldehyde concentration was determined using HPLC according to the method of Kozutsumi et al. [22] with some modifications. A XDB-C18 pre packed column (250 mm × 4.6 mm, 5 μm) (Agilent, CaliforniaUSA) was used at room temperature in this analysis. Quantitative determinations were performed at a flow rate of 1.0 mL/min using BUH-DNPH as an internal standard. The mobile phase consisted of methanol, acetonitrile and water (25:35:40). Both the ACH-DNPH and BUH-DNPH peaks were detected at an absorbance of 360 nm with a UV detector.

ADH, ALDH, MDA, SOD, CAT and GSH levels in the liver

The ADH, SOD, CAT activities and the MDA, GSH content in the liver tissue were measured using kits purchased from the Nanjing Jiancheng Bioengineering Institute (Nanjing, China). The protein content was measured using a Coomassie brilliant blue assay kit (Nanjing, China). ALDH activity was determined using commercial assay kits (K731, Biovision, California, USA) following the manufacturer's instructions. All of the measurements were performed in triplicates.

ADH and ALDH gene expressions

Total mRNA from liver tissue was prepared using a total RNA kit (Omega, USA) according to the manufacturer's instruction. Complementary DNA (cDNA) was generated using a high capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, USA). Quantification of ADH and ALDH mRNA expressions in the liver was performed using a 7300 Real Time PCR System (Applied Biosystems). The primers used for examining the mRNA expression of ADH and ALDH are listed in Table 1. The β-actin gene was used as an

internal standard gene for quantification. Real-time PCR was performed using a commercial RT-PCR kit (Applied Biosystems) following the manufacturer's instructions. The reaction mixtures were incubated for an initial denaturation at 95°C for 2 min, followed by 40 PCR cycles of 10 s at 95°C, 30 s at 56°C and 30 s at 72°C. The relative amount of each gene was calculated using the $2^{-\Delta\Delta CT}$ method [23]. Analysis was performed in triplicates.

Enzyme	Forward primer	Reverse primer
ADH1	5'-GAAAGCAACTTTTGTAGCCGA-3'	5'-ACTCCTACGACGACGCTTACA-3'
ALDH2	5'-AAAGGAGTGTTGAGCGAGCTA-3'	5'-AGACATCTTGAATCCACCGAA-3'
β-actin	5'-CGTGGGCCGCCCTAGGCAACCA-3'	5'-TTGGCCTTAGGGTTCAGGGGGG-3'

Table 1: Primers for ADH and ALDH mRNA expression.

Statistical analysis

All values are expressed as the mean ± standard deviation (±SD). Data were analyzed using one-way analysis of variance (ANOVA), followed by a post-hoc Dunnett's t-test using the SAS software. Differences of $p<0.05$ were considered significant.

Results

Righting reflex and the rate of intoxication in mice

As shown in Table 2, platycodin D-treated mice exhibited a longer latency period for the alcohol-induced loss of the righting reflex and a shorter latency period to recover the righting reflex, and these effects of platycodin D were dose-dependent ($p<0.05$). The rates of inebriation were significantly lower in the HDG than in the LDG ($p<0.05$).

Groups	Loss of the righting reflex (min)	Recovery of the righting reflex (min)	Rate of intoxication (%)
CG	37.41 ± 3.21^a	128.14 ± 6.79^a	100 ± 0^a
LDG	51.75 ± 3.50^b	88.25 ± 5.38^b	79.33 ± 4.04^b
HDG	67.67 ± 4.51^c	68.37 ± 4.06^c	60.33 ± 4.62^c

Table 2: Effects of platycodin D on righting reflex and rate of intoxication in alcohol-loaded mice.

The different letters in a column denote values that were significantly different ($p<0.05$).

Alcohol and acetaldehyde concentrations in serum

Serum alcohol and acetaldehyde concentrations in alcohol-loaded mice are shown in Figure 2. The concentrations of alcohol and acetaldehyde were not detected for the NG. The mice in the CG group showed asharply increased serum alcohol concentration at 0.5 h after alcohol loading and maintained this high level for an additional 30 min. The peak serum alcohol concentration was observed 1.0 h after alcohol exposure and then decreased in all of the experimental groups. Compared to the CG, the serum alcohol concentration in the platycodin D-treated groups (LDG and HDG) were decreased by 63.3%, 23.2%, and 13.8% in LDG and decreased by 74.5%, 50.9%, and 48.1% in HDG at 0.5, 1.0, and 2.0 h, respectively.

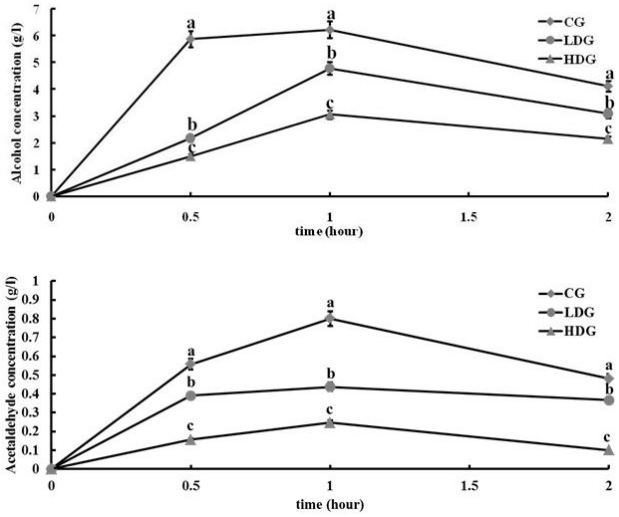

Figure 2: Changes of alcohol and acetaldehyde concentrations in alcohol-loaded mice for 2 hours. Values do not share the same letter are significantly different ($p<0.05$). The error bar represents standard deviation.

A significant difference in serum acetaldehyde concentration at 0.5 h after alcohol exposure was found in each group. The serum acetaldehyde concentration of each group showed a similar relationship to the change of serum alcohol concentration. Compared to the CG, the platycodin D-treated groups (LDG and HDG) were decreased by 29.9%, 45.4%, and 23.6% in LDG and decreased by 72.0%, 69.2%, and 79.0% in HDG at 0.5, 1.0, and 2.0 h, respectively.

ADH and ALDH activities

Compared to the CG, the ADH and ALDH activities of liver were remarkably increased by platycodin D treatments (Table 3). The ADH activity was elevated 1.41 and 2.40 times in LDG and HDG, respectively, and the ALDH activity was elevated 1.58 and 2.46 times in LDG and HDG, respectively. Meanwhile, compared to the LDG, the ADH and ALDH activities of the HDG were significantly increased ($p<0.05$).

ADH and ALDH expressions

The activities of ADH and ALDH in the liver were significantly reduced in the control group. Compared to the CG, the gene expression of ADH and ALDH in the platycodin D-treated groups significantly increased at 2.0 h after alcohol exposure ($p<0.05$). The gene expression of ADH was elevated 1.50 and 2.21 times in the LDG and HDG, respectively, and gene expression of ALDH was elevated 1.41 and 2.66 times in the LDG and HDG, respectively. In addition, compared to the LDG, ADH and ALDH gene expression was significantly higher in the HDG at 2.0 h after alcohol-loaded ($p<0.05$).

MDA, SOD, CAT and GSH levels in liver

Table 3 showed that administration of alcohol induced the significant increase of MDAby 26.2% in the control group ($p<0.05$) compared with the normal group, which was significantly attenuated by platycodin D treatments ($p<0.05$).

Groups	ADH (U/mg protein)	ALDH (U/mg protein)	MDA (nmol/mg protein)	SOD (U/mg protein)	CAT (U/mg protein)	GSH (μM/g protein)
NG	12.32 ± 0.33^b	2.35 ± 0.31^b	1.87 ± 0.03^c	17.34 ± 1.05^c	50.36 ± 2.02^c	190.24 ± 5.33^d
CG	10.06 ± 2.13^a	1.95 ± 0.51^a	2.36 ± 0.17^a	12.48 ± 0.75^a	34.50 ± 1.00^a	106.92 ± 13.27^a
LDG	14.20 ± 2.38^b	3.08 ± 0.47^b	2.08 ± 0.10^b	14.38 ± 0.82^b	40.50 ± 1.37^b	142.40 ± 8.24^b
HDG	24.13 ± 1.92^c	4.80 ± 0.94^c	1.89 ± 0.09^c	16.59 ± 0.76^c	48.84 ± 4.15^c	166.39 ± 13.89^c

Table 3: Effect of platycodin D on ADH, ALDH, MDA, SOD, CAT and GSH levels in liver. The different letters in a column denote values that were significantly different ($p<0.05$).

The antioxidants SOD, CAT and GSH were significantly reduced by alcohol exposure (Table 3). The platycodin D-treated groups had significantly increased SOD and CAT activities, and there was no significant difference in the final values between the platycodin D-treated groups and the NG ($p>0.05$). The GSH content of the LDG was also significantly elevated compared to the CG, but still evidently lower than the NG. In addition, the activity of CAT and SOD and the content of GSH were significantly higher in the HDG compared to the LDG ($p<0.05$).

Discussion

Platycodin D was isolated from the root of *P. grandiflorum* and showed liver-protective activity [18]. Here we report a relationship between platycodin D and alcohol metabolism. We show that platycodin D extended the latency period of loss of the righting reflex due to alcohol, shortened the recovery period of the righting reflex, and lowered the inebriation rate. Alcohol intoxication can be treated by natural plant extracts. For example, Lin and Li reported that puerarin, daidzin, and daidzein, the major isoflavones components of Pueraria lobata extracts, shortened the time of recovery of the righting reflex, suggesting that the anti-inebriation effects of Pueraria lobata extracts may be explained by the antioxidant activity of isoflavones [24].

Alcohol ingestion can result in hangover in animals, and acetaldehyde can cause diarrhea, nausea, and headache [25]. The alcohol and acetaldehyde concentrations in serum are usually used as a metric of alcohol intoxication. The present results showed that serum alcohol and acetaldehyde concentrations of platycodin D-treated groups were significantly lower than those of the control group (Figure 2). Moreover, the alleviating effects of high dose platycodin D after alcohol-loaded were considerably superior to those of the low dose. Promoting the metabolism of alcohol can protect against alcohol intoxication [26]. Thus, our result suggests that platycodin D could alleviate alcoholic intoxication by promoting alcohol and acetaldehyde metabolism.

Alcohol oxidation is a multistep process in which ADH and ALDH contribute to the oxidative metabolism of alcohol [27,28].Therefore, the activities of ADH and ALDH were measured in the liver following alcohol administration in mice. Platycodin D significantly increased the activities of ADH and ALDH. ADH and ALDH are important for alcohol metabolism. For example, Cho et al. reported that Evodiae fructus extracts could stimulate alcohol and acetaldehyde metabolism and increase the activities of ADH and ALDH in alcohol-loaded mice [29].The present results indicate that platycodin D accelerated alcohol and acetaldehyde metabolism by increasing ADH and ALDH activities. We also found that compared to the control group, the gene expression of ADH and ALDH in platycodin D-treated groups was increased 2.0 h after alcohol exposure, which is consistent with the observation that 2.0 h after alcohol exposure, alcohol and acetaldehyde concentrations were lower, and the activities of ADH and ALDH were higher in platycodin D-treated groups. Sung et al. observed that taraxerone treatment of alcohol-loaded mice could stimulate alcohol and acetaldehyde metabolism in serum. The activity and mRNA expression of ADH and ALDH in taraxerone-treated groups was also remarkably increased. Taraxerone stimulated alcohol metabolism via an increase of ADH and ALDH activity and gene expression [30]. This finding suggests that platycodin D promotes ADH and ALDH gene expression in alcohol-loaded mice.

Acute alcohol intoxication is always associated with an increase in lipid peroxidation and the production of radical-mediated oxidative stress (ROS) [31]. The hepaticMDA level is widely used as an indicator of lipid peroxidation and a major parameter for the status of oxidative stress [32]. Inhibiting ROS and MDA production and maintaining the normal function of antioxidant mechanisms are important for the protection of liver from alcohol exposure. In our study, acute alcohol administration caused an increase of hepatic MDA contents as compared to the normal group. Administration of platycodin D decreased the elevation of MDA level, especially in the HDG. The activity of SOD and CAT and the GSH content in liver were significantly declined in the control group, while the hepatic levels of these antioxidant enzymes were substantially increased in platycodin D-treated groups compared to the control group after 2 h. These results was consistent with a previous study of Sung et al. who reported that taraxerone could restore these hepatic antioxidant components in alcohol-loaded mice to the normal ranges after short periods [30]. SOD plays a vital role in removing O^{2-} and catalyzes O^{2-} dismutation to hydrogen peroxide (H_2O_2). Subsequently, H_2O_2 can be detoxified by the degradation of CAT and GSH in the liver [33,34]. Thus, that treatment with platycodin D may inhibit ROS, MDA production and maintain antioxidant mechanisms, whichwas consistent with previous studies of Liet al. [18].

Conclusion

Platycodin D extends the latency of the loss of the righting reflex and hastens the recovery period of righting reflex, lowers the inebriation rate, reduces alcohol and acetaldehyde concentrations in the serum, and induces the activity and mRNA expression of ADH and ALDH after alcohol intake. Moreover platycodin D prevented the decline of hepatic antioxidant enzymatic activity because of alcohol exposure. These results indicate that platycodin D has anti-inebriation properties; however, more studies with larger samples are needed to substantiate the effects of platycodin D on alcohol metabolism.

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