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RESEARCH NOTE

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Hepatoprotective Effects of Ginseng Intestinal Metabolite IH-901 on Chemical-Induced Hepatic Damage

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Abstract Hepatoprotective effects of white ginseng extract (WGE), and IH-901 (20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol) derived from intestinal metabolite of ginsenoside Rb_1 were studied using two experimental animal models with chemical-induced hepatic damage. Administration of WGE (200 and 500 mg/kg) and IH-901 (0.01, 0.05, and 0.1 mM/kg) significantly decreased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in acute hepatitic mice induced by CCl_4. Administration of WGE (100 mg/kg) and IH-901 (0.02, 0.04, and 0.08 mM/kg) significantly decreased AST and ALT levels in acute hepatitic rats induced by D-galactosamine. AST and ALT levels of IH-901 groups decreased. These results suggested WGE and IH-901 may have protective effects against chemical-induced hepatic damage.

Keywords: hepatoprotective effects, white ginseng, intestinal metabolite, IH-901

Introduction

Ginseng radix (*Panax ginseng* C.A. Meyer), one of the most important oriental herbal medicines, has been used to maintain physical vitality throughout the Far-Eastern countries since two thousand years ago. Shin-Nong-Bon-Tcho-Kyung, the oldest oriental medicine reference book, describes that ginseng can be used as a folk medicine to strengthen the activity of the five internal organs and vitalize stamina (1). More recently, the extensive biological activities of ginseng has also been revealed through systematic pharmacological investigations, including effects on the cardiovascular system (2), immune system (3), nervous system (4), activities of antidote (5), antitumor agent or antitumor adjuvant (6), and antidiabetic (7).

Ginseng radix contains various components such as saponins (ginsenosides), polyacetylenes, polysaccharides, phenolic compounds, proteins, and acidic peptides (4, 8, 9). Of the diverse constituents of ginseng, saponins have been found as the major components responsible for the biochemical and pharmacological actions of ginseng. Recently, Hasegawa et al. (10) found that the novel ginseng saponin metabolites formed by the human intestinal bacteria have antitumor activity. *Prevotella oris*, contained in 79% of the human fecal specimens, hydrolyzes ginsenoside Rb_1 and Rd into 20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol (IH-901, Compound K). According to Hasegawa et al. (11), IH-901, one of the metabolites detected in blood after the ginsenoside Rb_1 was orally administrated to mice, could be the major component of protopanaxadiol saponin absorbed from the intestine. Traditionally, ginseng-containing prescriptions have been known to be effective in the medicinal treatment of hepatitis. In fact, ginsenoside Ro as an oleanane-type ginseng saponin showed inhibitory effects on the acute hepatitic model induced by D-galactosamine (12). However, no experimental study has yet been performed on the beneficial effects of the ginseng intestinal metabolite (IH-901) and white ginseng on hepatitis. Therefore, the objectives of this study were to investigate hepatoprotective effects of white ginseng and IH-901 on chemical-induced hepatic damage in mice and rats.

Materials and Methods

Materials White ginseng (Ginseng radix alba) was extracted with 50% ethanol for 4 hr and concentrated in vacuum. IH-901 (Fig. 1) was biosynthesized by incubating ginseng saponins and intestinal bacteria using Hasegawa's

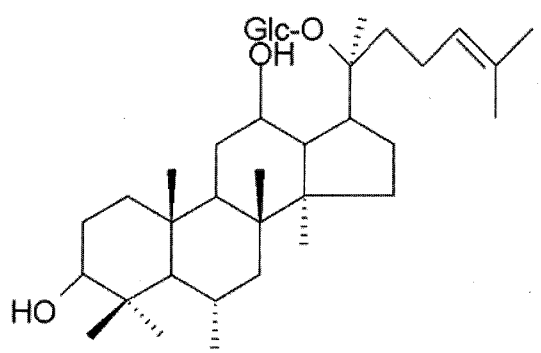

Fig. 1. Chemical structure of IH-901.

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method (10). D-Galactosamine (GalN), carbon tetrachloride (CCl_4), and other reagents were purchased from Sigma Chemical Co. (St. Louis, MO, USA).

Animal models Male Sprague Dawley rats (180 - 200 g each) and ICR mice (20 - 30 g each) were maintained in a temperature and light-controlled room (25±2°C and 12 hr, respectively). A laboratory pellet chow (Samyang Co., City, Korea) and water were provided freely.

CCl_4-induced acute hepatitis CCl_4 in corn oil (1 mL/kg) was injected intraperitoneally to the ICR mice 1 hr after the test substance (suspended in 0.2% CMCNa) had been administered orally for 7 days. The control group received the vehicle. The rats were anesthetized with diethyl ether, and whole blood samples were withdrawn from the eyes into pasteur pipettes 24 hr after the injection of CCl_4 (12). The AST and ALT levels were measured using the kits of Stanbio AST/GOT (Prueba-UV) and Stanbio ALT/GPT (UV-Rate) described in the Procedure Nos. 0920 and 0930, respectively (13).

GalN-induced acute hepatitis GalN in saline (400 mg/kg) was injected intraperitoneally to the S.D. rats 2 hr after oral administration of the test substance (suspended in 0.2% CMCNa or distilled water). The control group received the vehicle. The rats were anesthetized with pentobarbital (45 mg/kg, *i.p.*), and whole blood samples were withdrawn from the inferior vena cara into plastic syringes 24 hr after the injection of GalN (Matsuda et al., 1991). The AST and ALT levels were measured using kits of Stanbio AST/GOT (Prueba-UV) Procedure No. 0920 and Stanbio ALT/GPT (UV-Rate) Procedure No. 0930, respectively.

Data analysis Data were obtained through the descriptive analysis. Students *t*-test was performed to analyze the data. P-value less than 0.05 was determined as statistically significant (Ver. 11.5 SPSS).

Results and Discussion

Studies showed that acute hepatitis could be induced by the intraperitoneal injection of CCl_4 in corn oil (1 mL/kg), resulting in increased AST and ALT levels (Fig. 2.). Significant increases in the levels of AST and ALT were found in mice orally given IH-901 (0.01, 0.05 and 0.1 mM). In addition, the protective effects of white ginseng extract (WGE) were observed when WGE was administered orally at 50, 200, and 500 mg/kg into mice 1 hr before the injection of CCl_4; compared to the hepatitic control group, WGE significantly reduced AST (at 200 and 500 mg/kg) and ALT levels (at 50, 200, and 500 mg/kg) (Fig. 3.).

GalN induced acute hepatitis, resulting in the increased levels of AST and ALT (Fig. 4). When IH-901 (0.02, 0.04, and 0.08 mM/kg) were administered orally to rats 2 hr prior to the injection of GalN, the AST and ALT levels decreased significantly. WGE at 100 mg/kg significantly reduced AST levels compared to the control group. Furthermore, both 10 and 100 mg/kg of WGE significantly reduced ALT levels. On the other hand, silymarin as a standard significantly decreased both AST and ALT levels.

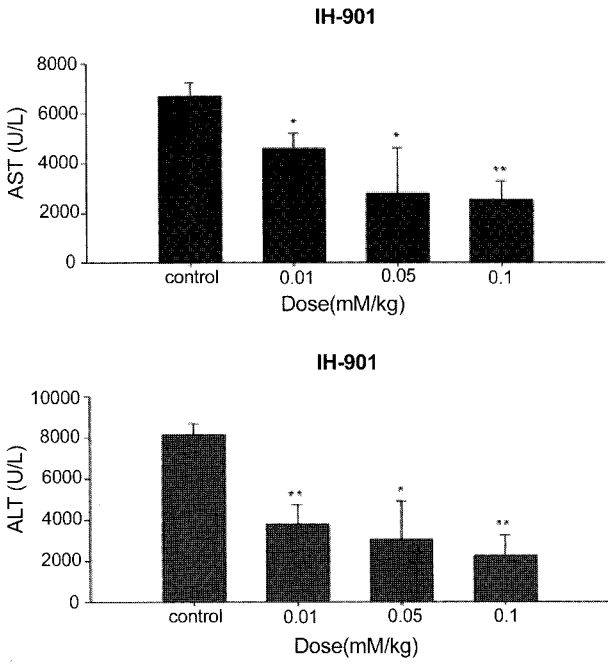

Fig. 2. Hepatoprotective effects of IH-901 on CCl_4-induced acute hepatitis. *p<0.05, **p<0.01. (n=6)

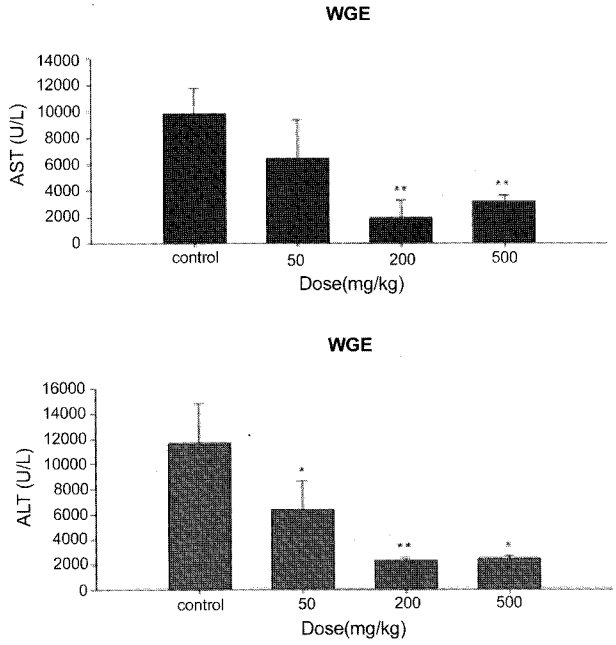

Fig. 3. Hepatoprotective effects of White Ginseng Extract (WGE) on CCl_4-induced acute hepatitis. *p<0.05, **p<0.01. (n =6)

So far, several experimental animal models of liver injury have been established using CCl_4, D-GalN, and D-GalN/LPS (14-16). However, this study is the first to reveal the protective effect of ginseng intestinal metabolite against acute liver injury in mice and rats.

Ginseng intestinal metabolite IH-901 was shown to have protective effect on liver damage in mice and rats treated with CCl_4 and GalN, suggesting that IH-901 may have hepatoprotective effects in the experimental animal models. Taken together, IH-901 showed comparable anti-

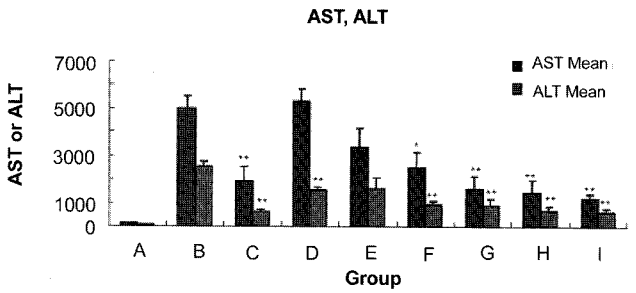

Fig. 4. Hepatoprotective effects of IH-901 and White Ginseng Extract (WGE) on GalN-induced acute hepatitis. A : Control, B : GalN (400 mg/kg), C : silymarin (0.05 mM/kg), D : WGE (10 mg/kg), E : WGE (50 mg/kg), F : WGE (100 mg/kg), G : IH-901 (0.02 mM/kg), H : IH-901 (0.04 mM/kg), I : IH-901 (0.08 mM/kg). C~I groups were orally administered followed by 2 hr-duration, the i.p. administration with the GalN (400 mg/kg) was given to S.D. rats. Silymarin, WGE and IH-901 were suspended in 2% carboxy methyl cellulose. $*p<0.05$, $**p<0.01$. (n=6)

hepatitic activities at the doses used in this study. Further studies on comparison of physiological activity between glycoside form and prosapogenin form will be performed in the near future. Silymarin also showed inhibitory activity on GalN-induced acute hepatitis in rats.However, IH-901 (0.02, 0.04, and 0.08 mM/kg) in terms of the AST level exhibited higher protective effects than silymarin (0.05 mM/kg) on liver damage in rats treated with GalN.

This study clearly demonstrated that IH-901 provides inhibitory effects on both CCl_4- and GalN-induced hepatic damages. The ginsenoside Ro, which is a ginseng saponin of the oleanane type, has already been found to have hepatoprotective effect (12). Because IH-901 was identified to have the hepatoprotective effect, we could therefore assume that the protopanaxadiol group of the dammarane type ginsenoside from *P. ginseng* has hepatoprotective effect. Therefore, this study justified the traditional use of ginseng as an oriental medicine for the remedy of hepatic disorders (1).

Acknowledgments

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