NOTE ***Surgery***

The Effect of Korean Red Ginseng on Liver Regeneration after 70% Hepatectomy in Rats

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ABSTRACT. The effect of Korean red ginseng (KRG) on morphologic change and function of the liver was investigated after 70% hepatectomy in rats. The liver weight and hepatocyte proliferation of the KRG treated groups significantly increased compared to those of the control group. KRG inhibited the increase of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and the number and area of lipid droplets. On the basis of these results, it could be concluded that KRG accelerated the liver regeneration and ameliorated liver injury after hepatectomy in rats.

KEY WORDS: hepatectomy, Korean red ginseng, liver regeneration.

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A hepatectomy may be indicated by hepatic neoplasia, abscess, injury, or vascular alteration [2]. A partial hepatectomy has been proved to be a useful animal model to study the various aspects of liver regeneration. The regenerative capacity of the normal liver is very well known. Following up to 70 to 90% partial hepatectomy, the original liver volume is regained within 10 to 14 days in rats [7]. The regenerative responses of the liver following removal of 70% of its mass provide a suitable *in vivo* model of cell proliferation.

The Ginseng root has been used for a long time, in the belief that it is a panacea and promotes longevity. The efficacy of ginseng was known in the West by the 18th century, and the study of ginseng has a long history [8]. Among the several kinds of Panax ginseng, Korean red ginseng (KRG) has efficacies such as anticancer [12], antihypertension [9], antidiabetes [14] and antinociception [15].

Although KRG has been investigated for multiple purposes, its effect on the regeneration of the liver has not yet been elucidated. The present study, therefore, was conducted to investigate the effect of KRG on morphologic change and function of the liver after 70% hepatectomy in rats.

Adult male *Sprague-Dawley rats* (weighing 230 to 290 g and aged 7 to 8 weeks) were used in this study. This study was approved by the Kyungpook National University Animal Ethics Committee.

The rats were divided into four groups: the sham group (n=20) in which a laparotomy was performed with no treatment, the control group (n=20) in which a 70% hepatectomy was performed with no treatment, the 250 group (n=20) in which a 70% hepatectomy was performed with an administration of 250 mg/kg of KRG, and the 500 group (n=20) in which a 70% hepatectomy was performed with an administration of 500 mg/kg of KRG.

Korean red ginseng (KRG, Cheong-Kwan-Jang) was purchased from the Korea Gingseng Corporation (Seoul, Korea). KRG was dissolved in 1L of distilled water, with a final concentration adjusted to 100 mg/m*l*. KRG (250 or 500 mg/kg body weight) was orally administered once a day from the day before the laparotomy was performed to the 9th day after a partial hepatectomy in the KRG treated groups.

Following an intraperitoneal injection of thiopental sodium (50 mg/kg), ventral abdominal wall hair was shaved and the field was scrubbed with alcohol solution. According to a previously described technique, a 70% hepatectomy was then performed [7].

Five rats in each group were sacrificed on days 1, 3, 7, and 10 postoperatively and their livers were excised and weighed. Immediately before sacrifice, blood was collected from the inferior vena cava under anesthesia for biochemical blood analysis.

Morphological liver regeneration was evaluated in terms of the restoration of liver weight (LW) in proportion to the body weight (BW). Liver weight: body weight ratio(%) was calculated by dividing the liver weight by the initial body weight before partial hepatectomy with a previous method by Grisham [5].

To evaluate the degree of postoperative liver injury, the levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and total bilirubin (T-Bil) in venous blood samples were determined.

After bleeding, samples from the liver were fixed in 10% neutral buffered formalin solution. After paraffin embedding, 4 sections were prepared. Representative sections of each tissue were stained with hematoxylin and eosin for light microscopic examination.

The number of mitotic cells (numbers/1,000 cells) and lipid droplets (numbers/mm^2), and the percentage of area

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occupied by lipid droplets were calculated using image analysis process (Soft Imaging System Corporation, Munchen, Germany).

All data were expressed as mean ± standard deviation. The comparisons for statistical significance among the groups were performed with the Mann-Whitney Wilcoxon's test.

The liver weight significantly increased on day 3, 7 and 10 in the 250 group, and on day 3 and 7 in the 500 group ($p<0.05$, Table 1), when compared with those in the control group. These results were in accordance with those in many previous reports that the liver weight after hepatectomy increased rapidly during the first three days [3, 7, 11, 13]. And it was observed that mitotic indices of the 250 and 500 groups on day 1 were about 4 and 6 times higher than those in the control group ($p<0.05$, Table 2). Thereafter, mitotic index declined gradually in the KRG treated groups. Similarly, the mean labeling index of the hepatocyte growth factor (HGF)-supplied livers at 24 hr after the hepatectomy was about 10 times higher than that of the control liver [10]. Thus, we used mitotic index and liver weight to assess the dynamic features of liver regeneration morphologically and histologically. From these data, it is evident that KRG significantly stimulates hepatocyte proliferation at a dose of 250 mg/kg in the rat.

We can consider two possibilities for this mechanism. The first is a direct trophic effect of KRG on hepatocytes. And the second possibility is that liver cells may be indirectly stimulated for mitosis through another pathway. As most pharmacological actions of ginseng are attributed to ginsenosides [4], it can be presumed that one or more ginsenosides seem to be beneficial in the liver regeneration. To clarify the effect of KRG on hepatocytes, further study is needed using different constituents of KRG with the same model or using molecular biological techniques.

In the present study, we found that levels of AST and ALT in all groups declined for 7 days after the hepatectomy and remained in lower levels until 10 days. There were significant statistical differences on day 3 in the 250 and 500 groups comparing with the control group ($p<0.05$, Table 3 and 4). The LDH levels on day 10 were lower in the 250 and 500 groups than in the control group, but the difference was not significant (Data not shown). The T-Bil levels were within normal range during the experimental period in all groups (Data not shown). As a result of these findings, it

Table 1. Effect of Korean red ginseng (KRG) on liver weight restoration in 70% hepatectomized rats

Group	LW/BW(%)			
	1	3	7	10 (day)
Sham	4.13 ± 0.50	3.68 ± 0.44	3.69 ± 0.42	3.57 ± 0.14
Control	1.50 ± 0.23	2.18 ± 0.22	2.39 ± 0.38	2.77 ± 0.30
250	1.61 ± 0.35	2.53 ± 0.44*	2.78 ± 0.29*	3.11 ± 0.30*
500	1.64 ± 0.33	2.56 ± 0.17*	2.87 ± 0.20*	2.99 ± 0.36

LW/BW(%); Liver weight/body weight ± 100. Sham; Only laparotomy. Control; 70% hepatectomy. 250; 250 mg/kg administration of KRG after 70% hepatectomy. 500; 500 mg/kg administration of KRG after 70% hepatectomy.Each value was expressed as mean ± standard deviation. *; $p<0.05$ compared with the control group.

Table 2. The effect of Korean red ginseng (KRG) on the number of mitotic cells in 70% hepatectomized rats

Group	Mitotic cell index (numbers/1000 cells)			
	1	3	7	10 (day)
Sham	0.60 ± 0.70	0.50 ± 0.71	0.60 ± 0.97	0.50 ± 0.85
Control	3.10 ± 1.66	5.30 ± 2.95	5.40 ± 2.01	8.80 ± 1.14
250	13.20 ± 3.91*	4.20 ± 2.49	2.50 ± 1.08	1.90 ± 0.99
500	19.50 ± 2.17*	7.20 ± 2.20	2.30 ± 1.06	0.60 ± 0.84

Keys see for Table 1.

Table 3. Effect of Korean red ginseng (KRG) on serum aspartate aminotransferase (AST) concentration in 70% hepatectomized rats

Group	AST (IU/L)			
	1	3	7	10 (day)
Sham	257.50 ± 105.36	53.50 ± 5.80	58.00 ± 31.82	27.33 ± 3.06
Control	512.40 ± 33.50	329.75 ± 75.24	64.60 ± 35.08	48.20 ± 17.66
250	434.20 ± 56.67	135.25 ± 48.61*	64.25 ± 37.90	50.20 ± 21.87
500	336.50 ± 137.37	95.50 ± 21.49*	72.20 ± 13.33	56.40 ± 18.17

Keys see for Table 1.

Table 4. Effect of Korean red ginseng (KRG) on serum alanine aminotransferase (ALT) concentration in 70% hepatectomized rats

Group	ALT (IU/L)			
	1	3	7	10 (day)
Sham	101.00 ± 97.58	33.75 ± 2.99	25.50 ± 9.33	10.56 ± 2.86
Control	368.60 ± 114.90	172.25 ± 66.41	17.80 ± 8.32	16.00 ± 9.82
250	308.20 ± 45.66	51.50 ± 23.33*	33.50 ± 27.04	12.60 ± 3.97
500	203.25 ± 113.64	49.25 ± 18.41*	26.00 ± 4.90	27.22 ± 11.23

Keys see for Table 1.

could be interpreted as indicating that the low levels of AST and ALT induced in the KRG treated groups may reflect the recovery in the remaining liver function due to the KRG administration. A number of studies have reported that serum transaminase levels were used as indicator of liver function [1, 3, 6, 16].

The number and area of lipid droplets were significantly lower in the KRG treated groups than in the control group ($p<0.05$ or $p<0.01$, data not shown). Consequently, it was demonstrated that a continuous KRG administration significantly inhibited the number and area of lipid droplets in the hepatectomized liver. As the previous studies showed that this hepatoprotective effect of ginseng was due to an antioxidative property of certain ginsenosides, we need to confirm these correlation, hereafter.

On the basis of our findings, we could conclude that KRG accelerated the rate of liver regeneration and ameliorated the liver injury after partial hepatectomy in rats. However, this issue warrants further investigation because a detailed study is needed to establish a mechanism between the KRG and hepatocyte proliferation after a hepatectomy.

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