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The Effects of Korean Red Ginseng (Ginseng *Radix Rubra*) on Liver Regeneration after Partial Hepatectomy in Dogs

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Abstract

We investigated the effects of the oral administration of Korean red ginseng (KRG) on morphologic change and function of liver in dogs. Fifteen adult mongrel dogs (n=15) were divided into three groups: a control group (40% hepatectomy, untreated), a 250 group (40% hepatectomy, 250 mg/kg of KRG, PO), and a 500 group (40% hepatectomy, 500 mg/kg of KRG, PO). The liver regeneration, histologic findings, CBC (WBC, RBC, PCV, and PLT), and liver function tests (AST, ALT, GGT, ALP, LDH, and T-bil) were examined during experiment. The liver regeneration rates were higher in treated groups than in the control group. But, there were no significant differences. All hematological values were within normal ranges except leukocyte counts for 3 days postoperatively. The levels of AST and ALT in the treated groups were significantly decreased compared to that in the control group ($p<0.05$). The numbers of degenerative cells and area of connective tissue were significantly decreased in the liver of the dog with KRG administration ($p<0.01$). On the basis of these results, we could conclude that KRG accelerate the liver regeneration and ameliorate the liver injury after hepatectomy in dogs.

Key words: liver regeneration, hepatectomy, Korean red ginseng, dog

Introduction

Hepatectomy may be indicated by hepatic neoplasia, abscess, injury, or vascular alteration [3]. Partial hepatectomy in dogs and rats has been proved to be a useful animal model to study the various aspects of liver regeneration. Several techniques were well standardized in rats and dogs [8, 20].

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In dogs, 40% heaptectomy is equal to resection of left lateral and left medial lobes [40]. It has been studied that many growth factors and cytokines seemed to play important roles in the process of liver regeneration.

Among the several kinds of Panax ginseng, Korean red ginseng (KRG) has efficacies such as anticancer [29], antihypertension [19, 22], antidiabetes [35], antinociception [41], and improving weak body conditions as tonics [24].

Active constituents found in most ginseng species include ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids. Recent studies showed the major active ingredients of ginseng to be a group of ginsenosides, and their chemical structures have been established [39].

Recently, it was known that oral administration of ginseng extract reduced serum total cholesterol and triglycerides inducing fatty liver after hepatic resection [5]. Panax ginseng extract could improve the atherosclerotic condition associated with hepatectomy by decreasing platelet adhesiveness [6]. It was reported that red ginseng could partially recover the hepatotoxicity induced by carbon tetrachloride in rats [23] and inhibit the increase of serum glutamic oxaloacetic transaminase (s-GOT) and serum glutamic pyruvic transaminase (s-GPT) levels in acute hepatitic rats [31].

Although KRG has been investigated for multiple purposes, its effect on the regeneration of the liver has not yet been elucidated. Therefore, the present study was conducted to investigate the effects of oral administration of KRG on morphologic change and function of the liver after partial hepatectomy in dogs.

Materials and Methods

1. Animals

Fifteen adult mongrel dogs of either sex (weighing 2.5 5.1 kg and aged 1 3 years) were used in this study. They were fed on pellet chow and tap water ad libitum. The animals were divided into three groups: the control group (n=5) in which 40% hepatectomy was performed with no treatment, the 250 group (n=5) in which 40% hepatectomy was performed with an administration of 250 mg/kg of KRG, and the 500 group (n=5) in which 40% hepatectomy was performed with an administration of 500 mg/kg of KRG.

2. Materials

KRG extract (Cheong-Kwan-Jang®) was purchased from Korea Gingseng Corporation, and dissolved in 1L of distilled water, with a final concentration adjusted to 100 mg/ml.

KRG (250, 500 mg/kg body weight) was orally administered once a day from day -1 to day 7 after 40% hepatectomy in the KRG treated groups.

3. Surgical procedure

Each dog was premedicated with atropine sulfate (0.05 mg/kg, IM, Kwangmyung Pharm Corp., Korea) at least 10 minutes before induction of anesthesia. Anesthesia was induced with thiopental sodium (10 mg/kg, IV, Penthotal sodium®, Choongwae Pharm Corp., Korea). Then, the trachea was intubated with a cuffed tube, and general anesthesia was maintained with isoflurane (Forane®, Choongwae Pharma Corp., Korea) in nitrous oxide and oxygen. Antibiotic (Cephalexin®, Dongwha Pharm Corp., Korea) and perioperative intravenous fluid (10 ml/kg/hr, Lactated ringer's solution) were administered.

The dogs were positioned in dorsal recumbency, and the abdomen was prepared for aseptic surgery. A cranial ventral midline celiotomy was performed, and the falciform ligament was reflected to the right. The left triangular ligament was transected to free the left lateral liver lobe from its attachment to the diaphragm. The left lateral and medial lobes were reflected out of the abdominal cavity, and doubly ligated with 2-0 polyamide suture materials (Supramid®, BRAUN, Germany) in the division between those and others lobes. And then, 40% of the total liver was removed by resecting the left lateral and left medial lobes. The linea alba was sutured with 2-0 polyglycolic acid (SURGISORB®, Samyang Co., Korea) in simple continuous pattern, the subcutaneous tissues with 3-0 polyglycolic acid (SURGISORB®, Samyang Co., Korea), and the skin with 2-0 polyamide suture materials (Supramid®, BRAUN, Germany) in simple interrupted patterns. In this way, the 40% hepatectomy was performed without any massive blood loss by ligating and cutting the pedicles.

The dogs were housed in individual cages. Surgical site was dressed with povidone-iodine and antibiotic (Cephalexin®, Dongwha, Korea) was administered throughout the postoperative period.

4. Sample collection and test items

All animals were sacrificed at 8 days after hepatectomy and their livers were excised and weighed. The rate of liver regeneration was calculated by comparing liver wet weights before and after hepatectomy according to the formula by Ito and Higashiguchi [21].

Rate of liver regeneration(%)

={(Liver weight at sacrifice 8 days postoperatively − Estimated weight of the remnant liver at the time of hepatectomy)} / Weight of the resected liver × 100

Blood samples were collected through jugular punctures from animals on days -1, 1, 3, 5, and 7 after hepatectomy. Approximately 1 ml and 1.5 ml of external jugular venous blood were used for complete blood count (WBC, RBC, PCV, and PLT) and biochemical analysis (AST, ALT, GGT, ALP, LDH, and T-Bil), respectively.

Liver specimens were fixed in 10% neutral-buffered formalin, embedded in paraffin, and cut into sections. For histological analysis, sections were stained with hematoxylin & eosin (H&E).

5. Statistical analysis

All data were expressed as mean±standard deviation. The comparisons for statistical significance among groups were performed with the Student's *t*-test. P values less than 0.05 were considered significant.

Results

1. Morphologic liver regeneration rates

The regeneration rates of liver at 8 days after hepatectomy were 62.24±18.79, 88.17±32.55 and 87.86±34.15 (%), for the control, 250 and 500 groups, respectively. They were higher in the KRG treated groups than in the control group. But there were no significant differences (Fig. 1).

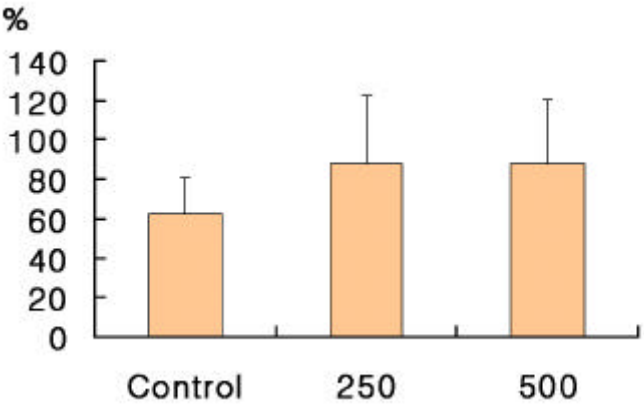

Fig. 1. Effect of Korean red ginseng on liver regeneration rate in 40% hepatectomized dogs.

2. Hematologic values

The counts of WBC on day -1 after hepatectomy were within normal ranges. The numbers of leukocytes increased during postoperative 3 days in all groups, but there were no significant differences among the groups. However, the counts of WBC tended to decline in all groups 3 days or more after hepatectomy without any significant differences (Table 1).

The Values of RBC, PCV and PLT on day -1 after hepatectomy were within normal ranges. They were slightly decreased in all groups postoperatively, but were in normal ranges and did not differ significantly at any perioperative time point in all groups (Table 2, 3, 4).

Table 1. Effect of Korean red ginseng(KRG) on the WBC counts in hepatectomized dogs

Groups	After 40% hepatectomy (days)				
	−1	1	3	5	7
Control	10.25±3.62†	23.73±10.59	25.45±4.37	20.13±5.80	16.15±9.70
250	9.07±0.55	24.03±8.60	21.53±3.35	22.24±4.65	17.40±2.18
500	10.78±2.17	21.60±3.45	21.90±5.80	19.35±6.15	13.53±4.89

† Mean±S.D., 10³/μℓ

Table 2. Effect of KRG on the RBC counts in hepatectomized dogs

Groups	After 40% hepatectomy (days)				
	−1	1	3	5	7
Control	6.79±0.97†	5.98±1.31	6.45±0.96	5.96±0.80	6.06±0.87
250	5.92±1.44	5.55±0.30	5.81±0.61	6.09±0.09	6.10±0.09
500	7.00±1.67	5.57±0.26	5.92±1.03	6.26±0.59	5.69±0.35

† Mean±S.D., 10⁶/μℓ

Table 3. Effect of KRG on the PCV values in hepatectomized dogs

Groups	After 40% hepatectomy (days)				
	−1	1	3	5	7
Control	44.93±7.76†	40.83±9.78	41.10±6.81	43.70±6.36	37.48±7.44
250	42.68±5.41	35.20±1.76	36.67±4.56	41.33±1.37	41.40±0.53
500	41.48±7.54	37.78±5.99	38.75±5.48	42.05±2.36	39.60±1.41

† Mean±S.D., %

Table 4. Effect of KRG on the PLT counts in hepatectomized dogs

Groups	After 40% hepatectomy (days)				
	−1	1	3	5	7
Control	414.00±111.87†	359.50±82.79	394.50±151.44	447.50±287.79	402.00±173.75
250	436.00±52.05	361.33±24.91	385.67±10.12	429.33±9.02	426.33±145.93
500	455.50±173.89	361.50±139.53	381.75±224.15	472.00±178.41	470.50±175.01

† Mean±S.D., 10³/μℓ

3. Serum chemistry values

The levels of AST on day -1 after hepatectomy were within normal ranges. The levels of AST were showed on day 1 after hepatectomy the peak in all groups, but no significant differences were found among the groups. And then, the levels of AST tended to decline in all groups, and remained low in the treated groups compared to those in the control group 3 days or more after hepatectomy, but there were no significant differences (Table 5).

The levels of ALT on day -1 after hepatectomy were within normal ranges. The levels of ALT, 1 day after hepatectomy, showing increases in all groups and peaks in the KRG treated groups, but no significant differences were found among the groups. And then, the levels of ALT tended to decline sharply and remained low in treated groups compared to those in the control group 3 days or more after hepatectomy. In the 500 group, the level of ALT significantly ($p<0.05$) decreased compared to that in the control group on day 5 after hepatectomy (Table 6).

The levels of GGT on day -1 after hepatectomy were within normal ranges. The levels of GGT, 1 day after hepatectomy, showing the peak in all groups, but no

significant differences were found among the groups. And then, the levels of GGT tended to decline in all groups 3 days or more after hepatectomy, but there were no significant differences (Table 7).

The levels of ALP on day -1 after hepatectomy were within normal ranges. There were increases on day 1 and 3 in all groups, but no significant differences were found among the groups. And then, the levels of ALP tended to decline in all groups 3 days or more after hepatectomy, but there were no significant differences (Table 8).

The levels of LDH on day 1 after hepatectomy were increased in all groups, but no significant differences were found among the groups. And then, the levels of ALP tended to decline in all groups 1 day or more after hepatectomy, but there were no significant differences (Table 9).

The levels of T-Bil on day -1 after hepatectomy were within normal ranges. The levels of T-Bil in the 500 group were higher than those in the control and 250 group on days 1 and 3 after hepatectomy, but no significant differences were found among the groups. All values were within normal ranges in all groups during experimental period (Table 10).

4. Histological findings

Histologically, increase of ballooning cells (swelled cells) and deposition of connective tissue in the portal triad portions of the hepatic lobules were demonstrated in the hepatectomized liver.

Severe to moderate frequent degenerations of hepatic cells (ballooning or swelling) were observed throughout whole liver parenchyma in the control group (Fig 1). These abnormal histological signs were detected in all groups, but the degrees in the KRG treated groups were less severe than in the control group (Figs 2, 3).

The number of degenerative cells on day 8 after hepatectomy were 99.30±1.06, 85.20±7.51, and 64.10±10.40 for the control, 250, and 500 groups, respectively. When the number of the 250 and 500 groups were compared to those in the control group, there were significant ($p<0.01$) statistical differences (Table 11).

The percentage area of occupied by connective tissue on day 8 after hepatectomy were 20.86±5.11, 8.86±1.86, and

Table 5. Effect of KRG on the serum AST concentration in hepatectomized dogs

Groups	After 40% hepatectomy (days)				
	-1	1	3	5	7
Control	13.33±2.52†	570.50±430.64	332.25±75.70	172.50±144.81	97.00±61.68
250	11.67±4.73	410.33±352.76	94.00±64.86	70.33±19.40	37.33±8.33
500	11.75±2.36	483.75±441.81	56.50±29.33	21.00±15.56	24.75±14.57

† Mean±S.D., IU/L

Table 6. Effect of KRG on the serum ALT concentration in hepatectomized dogs

Groups	After 70% hepatectomy (days)				
	−1	1	3	5	7
Control	33.33±19.73†	623.25±435.12	884.75±230.50	777.00±317.27	640.25±429.06
250	25.33±17.24	984.33±27.14	638.67±81.84	404.33±46.36	389.67±54.99
500	17.50±6.76	627.75±298.26	518.00±357.96	257.50±350.02*	270.50±82.71

† Mean±S.D., IU/L

*$p<0.05$ compared to those in the control group by Student's t-test

Table 7. Effect of KRG on the serum GGT concentration in hepatectomized dogs

Groups	After 40% hepatectomy (days)				
	−1	1	3	5	7
Control	10.00±0.00†	29.75±11.84	26.67±2.52	21.25±13.30	15.75±10.84
250	10.00±0.00	46.25±26.76	22.75±16.68	22.00±12.53	11.75±3.50
500	10.33±0.58	34.67±10.97	20.33±9.71	17.25±8.38	13.50±3.70

† Mean±S.D., IU/L

Table 8. Effect of KRG on the serum ALP concentration in hepatectomized dogs

Groups	After 40% hepatectomy (days)				
	−1	1	3	5	7
Control	80.25±28.04†	186.00±157.47	457.25±265.20	303.50±75.66	293.00±101.41
250	107.67±67.88	216.67±115.94	361.00±85.35	332.33±124.64	329.67±119.24
500	57.67±13.28	281.25±306.96	382.75±263.27	345.25±152.48	291.75±138.15

† Mean±S.D., IU/L

Table 9. Effect of KRG on the serum LDH concentration in hepatectomized dogs

Groups	After 40% hepatectomy (days)				
	−1	1	3	5	7
Control	193.75±82.77†	392.50±130.81	266.00±172.53	135.00±21.21	146.00±46.67
250	125.00±22.11	314.00±105.30	147.00±52.09	140.33±36.83	157.00±43.97
500	181.00±130.04	356.75±178.37	180.50±45.41	154.00±75.44	155.50±78.95

† Mean±S.D., IU/L

Table 10. Effect of KRG on the serum T-Bil concentration in hepatectomized dogs

Groups	After 40% hepatectomy (days)				
	−1	1	3	5	7
Control	0.40±0.08†	0.33±0.13	0.28±0.10	0.35±0.07	0.25±0.06
250	0.37±0.06	0.37±0.06	0.30±0.00	0.27±0.06	0.20±0.00
500	0.40±0.10	0.50±0.40	0.45±0.38	0.30±0.08	0.25±0.06

† Mean±S.D., mg/dl

Table 11. Effect of KRG on the number of degenerative cells and the area of occupied by connective tissue in hepatectomized dogs

Groups	Day 8 after 40% hepatectomy	
	Numbers of degenerative cells (number/100 cells)	Connective tissue occupied area (%)
Control	99.30±1.06†	20.86±5.11
250	85.20±7.51*	8.86±1.86*
500	64.10±10.40*	6.16±1.89*

† Mean±S.D.
* $p<0.01$ compared to those in the control group by Mann-Whitney Wilcoxon's test

6.16±1.89 (%) for the control, 250, and 500 groups, respectively. When the percentage area of 250 and 500 groups were compared to those in the control group, there were significant ($p<0.01$) statistical differences (Table 11).

Discussion

Partial hepatectomy is often used to study liver regeneration because it is less associated with tissue injury and inflammation than cirrhotic model induced by hepatic toxic materials. Kameoka et al [26] reported that the resection of the left lateral and left medial lobes is equal to 40% partial hepatectomy in the dog. It was also reported that 55% hepatectomy was used to investigate the properties of glycosaminoglycans (GAGs) in the regenerating liver of mongrel dogs and performed by resecting the right medial,

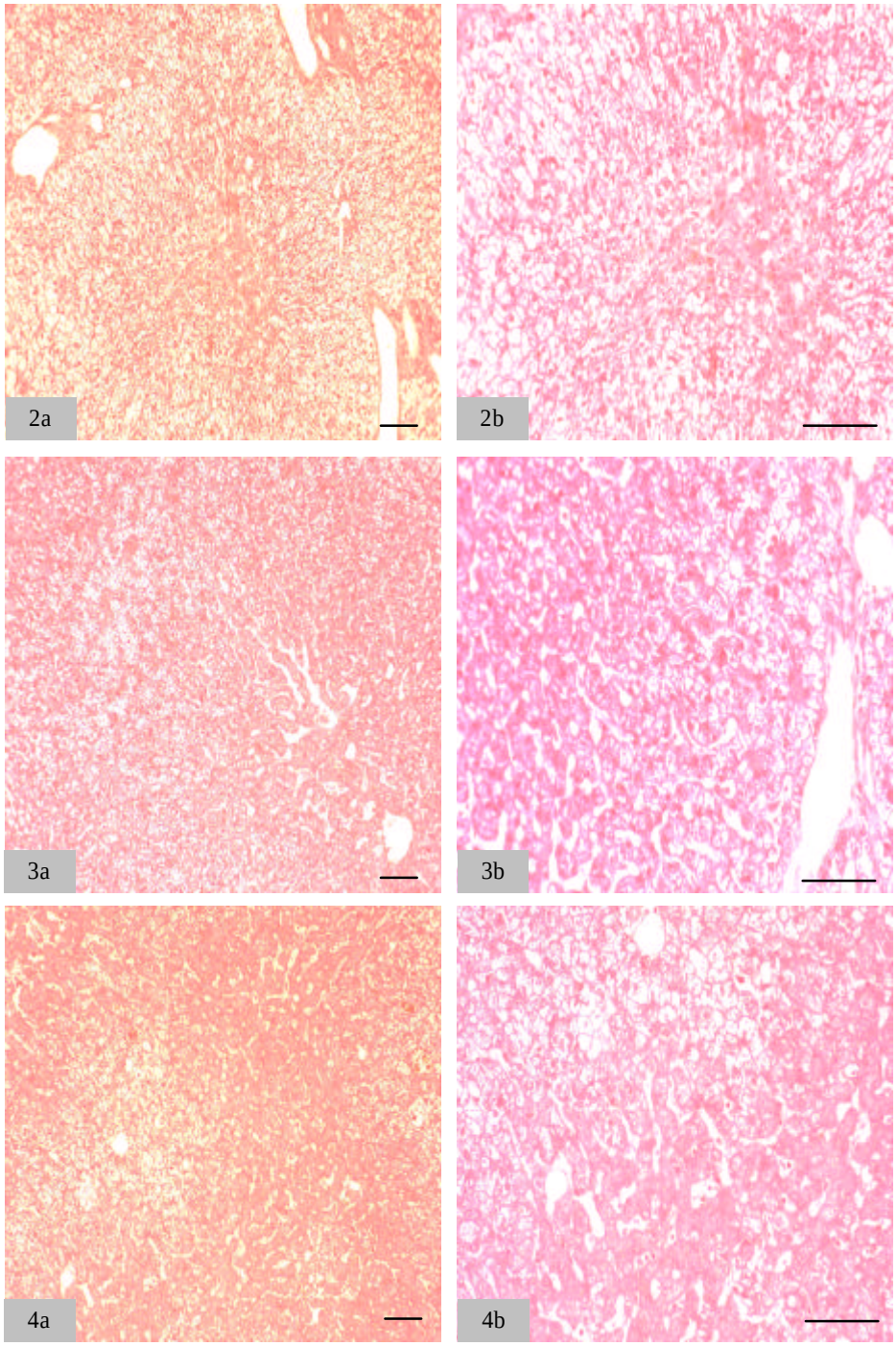

Fig. 2. Control group; degenerated cells were demonstrated throughout whole liver parenchyma.
a, ×50; b, ×1004. Hematoxylin-Eosin stain. Bar indicates 100 ㎛.

Fig. 3. 250 group; degenerated cells and relatively intact cells were intermingled with each other, and the zone of the degenerative cells was clearly differentiated.
a, ×50; b, ×100. Hematoxylin-Eosin stain. Bar indicates 100 ㎛.

Fig. 4. 500 group; degenerated cells and relatively intact cells were intermingled with each other, and the zone of the degenerative cells was clearly differentiated. More numerous intact cells were demonstrated compared to those of the 250 group.
a, ×50; b, ×100. Hematoxylin-Eosin stain. Bar indicates 100 ㎛.

right lateral, quadrate, and caudate lobes [43]. Nagao et al [33] investigated the mechanism of remnant liver dysfunction after 84% hepatectomy in canine model, which was consisted of resection of five lobes ; LL, LM, Q, RM, and C. In the present study, 40% hepatectomy by resection the left lateral and left medial lobes was utilized in dog study on the basis of these previous studies.

Normal liver has a very well known capacity for regeneration after up to 90% partial hepatectomy [10, 15, 20]. In human, it takes about 3 weeks for partially hepatectomized liver to regain its original volume [9]. It was also reported that the original volume is regained within 14 days in dogs [8]. Under normal conditions, hepatocytes have a very low regeneration rate ; therefore, almost no mitotic activity and BrdU incorporation into newly synthesized DNA could take place. However, partial hepatectomy triggers a rapid proliferation that tends to compensate the parenchymal loss [47]. In response to partial hepatectomy, hepatocytes sufficient enough to restore the original hepatic mass in individuals enter the cell cycle and progress to DNA synthesis and replication.

In previous studies, it has been showed that many factors play important roles in the process of liver regeneration. These include interleukin-6 [38], gastrin [37], cyclosporin A [28, 32], prostaglandin E2 [45], vitamin D [7], vitamin E [16], α-tocopherol [2], and tacrolimus (FK506) [36, 42]. The effects of vitamin E deficiency on inhibition of liver regeneration and the influence of dietary vitamin E on lipid peroxidation and liver regeneration in partially hepatectomized rats have previously been studied and the beneficial effects of vitamin E on liver regeneration has been pointed out [16].

Panax ginseng is considered as one of the most valuable natural tonics in the East as well as the West. It has also been used in the Orient for over 2000 years for prevention and treatment of various diseases. Over the last decade, researchers have found that panax ginseng could exert beneficial effects on the cardiovascular system via its antiischemic, antihypertensive, and antioxidative actions [4, 17, 19, 27, 48].

Active constituents found in most ginseng species include ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids. There is a wide variation (2-20%) in the ginsenoside content of different species of ginseng. Most pharmacological actions of ginseng are attributed to ginsenosides. More than twenty ginsenosides have been isolated [17], and single ginsenosides have been shown to produce multiple effects in the same tissue [34, 44].

Among the several kinds of Panax ginseng, KRG has several pharmacological and physiological effects that are being gradually disclosed. In particular, saponin fraction of KRG shows a variety of efficacies such as anticancer [29], antihypertension [22], antidiabetes [35], antinociception [41], and improving weak body conditions as tonics [24]. However, the effect of KRG on the liver regeneration after partial hepatectomy in dogs is still unknown. Therefore, in the present study, we attempted to examine the effect of KRG on liver regeneration.

Liver regeneration can be assessed by different tissue-based indices such as liver weights, mitotic counts, DNA contents and synthesis rates, immunohistochemical staining of nuclear antigens, gene expressions, and certain protein levels or various serum based tests that consist largely of specific enzyme determinations or documentations of certain proliferation markers. Andiran et al [2] reported that α-tocopherol administration seemed to improve the rates of regeneration in cirrhotic rats with respect to the bromodeoxyuridine (BrdU) incorporation, proliferating cell nuclear antigen (PCNA) labeling, and mitotic indices. But they didn't report which indices was more useful among them.

The assessment of liver regeneration rates obtained by Ito and Higashiguchi [21] demonstrated a difference in rates between the groups on day 8 after evisceration. The regeneration rate of liver on day 8 after hepatectomy were 62.24±18.79, 88.17±32.55, and 87.86±34.15 (%) for the control, 250, and 500 group, respectively. In the present study, it was showed that the regeneration rates were higher in the KRG treated groups than in the control group. But, there were no significant differences. On the basis of this finding, it could be supposed that the difference of liver regeneration was due to continuous KRG administration in dogs.

All hematological values (WBC, RBC, PCV, and PLT) were within normal ranges except the counts of leukocyte for 3 days postoperatively. Consistent with these our findings, Jeong et al [23] reported that the administration of saponin changed neither body and organ weight nor hematological and serum clinical parameters.

The levels of AST and ALT in the KRG treated groups were significantly ($p<0.05$) decreased compared to those in the control group on day 3 and 5 after hepatectomy, respectively. The levels of GGT and LDH on day 1 after hepatectomy, showed the peak in all groups, but no significant differences were found among the groups. And then, the levels of GGT and LDH tended to decline in all groups for 3 days or more after hepatectomy, but there were no significant differences. The levels of ALP in all groups were increased on day 1 after hepatectomy, showed the peak in all groups on day 3 after hepatectomy, but no significant differences were found among the groups. And then, the levels of ALP tended to decline in all groups for 5 days or more after hepatectomy, but there were no significant differences. The levels of T-Bil in all groups were within normal ranges during all experiment period, and there were not significant differences.

As a rusult of these findings, it 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, 12, 13, 14, 18, 30]. In previous studies, the levels of AST and ALT were most frequently measured to screen liver function, and various results have been reported. We could think that the reason is different animal, experiment, and hepatocyte growth factors.

Lipocytes in normal liver are distinguished by prominent intracellular droplets that contain vitamin A. Lipid droplets occur in all mammalian cell types and serve as energy storage site. They consist of a core of triacylglycerols and cholesterol esters, which are synthesized in the Endoplasmic Reticulum (ER), surrounded by a phospholipid monolayer, which is also derived from the ER [46]. The hepatic lipocyte (also known as the stellate, fat-storing, or Ito cell) has now been clearly identified as the primary cellular source of matrix components in chronic liver damage. In hepatic injury, lipocytes were activated by stimulated proliferation and fibrogenesis [11].

Liver fibrosis is a common response to chronic liver injury from many causes, characterized by a marked accumulation of extracellular matrix components within the perisinusoidal space of Disse. Perioperative HGF administration histologically improved liver fibrosis by reduction of fibrous connective tissue and liver damage consisting of hemorrhagic necrosis, congestion, and inflammatory cell infiltration [25].

Histologically, there were significant ($p<0.01$) decreases of the number of degenerative cells and area of connective tissue in the KRG administered and hepatectomized liver in the dog. This is in agreement with Kaido et al's [25] findings in the rat. Consistent with our findings, it was also demonstrated an effect of ginsenoside R0 on inhibition of the increase of connective tissue in the liver of CCl4 induced chronic hepatitic rats [31]. These findings suggested that KRG would protect hepatocytes from postoperative liver injury.

We examined differential features of liver regeneration induced in animals with hepatectomy and oral administration of KRG using morphological, functional, and histological examination. 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 dogs. However, this issue warrants further investigation because a detailed time course study is needed to establish a causal relationship between the KRG and mechanism of hepatocyte proliferation in the earlier phase after hepatectomy. Also, it may be interesting to see KRG how to be applied in clinical practice. Our present findings may contribute to establishing administration of KRG during and after hepatectomy to help stimulate the liver regeneration. Further studies are required to determine whether KRG also might stimulate cultured hepatocyte *in vitro*.

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