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Three Month Subacute Toxicity Study of *Ginkgo Biloba* Extract(EGb 761) in Rats

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ABSTRACT : *Group of 40 male and 40 female Sprague-Dawley rats was given daily intravenous injections of different dosage of Ginkgo biloba extract(EGb 761), 7.5 mg/kg/day (low dosage group), 15 mg/kg/day (middle dosage group), or 30 mg/kg/day (high dosage group) for 3 month by tail vein according to Established Regulation of Korean National Institute of Safety Research (1994. 4. 14). Appearance, behavior, mortality, and food consumption of rats of treated groups were not affected during the experimental periods. No significant Ginkgo biloba extract(EGb 761)-related changes were found in urinalysis, hematology, serum chemistry, and organ weight. No histopathological lesions were seen in both control and treatment groups. Our results strongly suggest that no toxic changes were found in rat treated intravenously with Ginkgo biloba extract(EGb 761) for 3 month.*

Key Words : *Ginkgo biloba extract(EGb 761), Rat*

I. INTRODUCTION

Ginkgo biloba extract made of leaves of Ginkgo tree (*Ginkgo biloba Linne*) plays a role as antagonist of platelet activating factor and have a function as microvascular permeability and bronchoconstriction (Chung K. F., *et al.*, 1987). In addition, *Ginkgo biloba* extract stimulates blood flow in arteries, capillaries, and veins (Jos K. *et al.*, 1992). Therefore, *Ginkgo biloba* extract pays attention to treatment of circulatory disorders (Jos K. *et al.*, 1992). Recently, *Ginkgo biloba* extract treated with cerebral dysfunctions such as loss of memory, dizziness, and headache in aging people (Semlitsch H. V., *et al.*, 1995). In Germany, *Ginkgo biloba* extract was widely used for cerebral dysfunction from early 1990 (Jos K. *et al.*, 1992). It has been reported that there were no side effect and drug interaction between other dugs in toxicity tests for *Ginkgo biloba* extract (DeFeudis F. G. *et al.*, 1991).

The present study was examined to investigate subacute toxicity, by giving rat injected with *Ginkgo biloba* extract(EGb 761) from YuYu Co., Ltd. for 3 month according to Established Regulation of Korean National Institute of Safety Research (1994. 4. 14).

II. MATERIALS AND METHODS

1. *Ginkgo biloba* Extract(EGb 761)

Ginkgo biloba extract(EGb 761) used in this study was supplied by YuYu Co., Ltd. *Ginkgo biloba* extract(EGb 761) was made of leaves of Ginkgo tree (*Ginkgo biloba Linne*). It was a brown crystalline powder and contained 25.3% Ginkgoflavonglycosides.

2. Experimental Animals

One hundred Sprague-Dawley rats, 50 male and 50 female, respectively, were purchased from Laboratory Animal Center at Seoul National University. The rats were acclimated to laboratory conditions for 7 days prior to assignment to the study. 40 male and 40 female rats were selected for experiment. Rats were housed on wood shaving in

transparent polycarbonate boxes (26×42×18 cm, MyoungJin Company, Republic of Korea) and maintained at anambient temperature (23±3°C), a relative humidity of 40-60% (50±10°C) with a minimum of 10 complete changes of 100% conditioned fresh air per hour, and a light/dark cycle of 12 hour light (from 7:00 AM to 7:00 PM) and 12 hour dark with no twilight. Rodent chow and water were available ad libitum throughout the experimental period.

3. Experimental Design

Forty male Sprague-Dawley rats were randomly assigned to three treatment groups and one control group. Also, forty female Sprague-Dawley rats were randomly assigned to three treatment groups and one control group. In each treatment group, rats were given daily intravenous injections of different dosage of *Ginkgo biloba* extract(EGb 761), 7.5 mg/kg/day (low dosage group), 15 mg/kg/day (middle dosage group), or 30 mg/kg/day (high dosage group) for 3 month by tail vein.

General conditions such as appearance, behavior and toxic signs were observed daily on all the rats as described in Established Regulation of Korean National Institute of Safety Research (1994. 4. 14). Body weight and feed consumption were recorded regularly. Trials to collect urine was performed one time by artificial urination during the whole experiment.

All rats were esanguinated from the abdominal aorta under light anesthesia by ether. Blood samples were collected from abdominal aorta into ethylenediaminetetraacetic acid (EDTA)-containing tubes for hematology and serum chemistry. At autopsy, gross lesions were recorded. Weights of liver, spleen, kidney, adrenal gland, heart, lung, salivary gland, brain, and testis were measured, fixed with 10% neutral buffered-formalin and embedded in paraffin. Tissues were routinely processed and sectioned (5 μm). Tissues were deparaffinized with xylene, rehydrated through traded alcohols, air dried and stained with hematoxylin and eosin.

Data were analyzed by non-parametric one way Kruskal-Wallis test, Terpstra-Jackheere test and Chi-square test.

III. RESULTS

1. Clinical Signs

The intravenous injection of *Ginkgo bibola* extract(EGb 761) developed no adverse effect on normal behavior of the animals in treatment and control group throughout the whole experiment. No dose-related death of rats was observed during the 3 month experimental period.

2. Body Weight

No significant difference body weight between *Ginkgo biloba* extract(EGb 761)-treatment and control group (Figs. 1 and 2).

3. Feed and Water Consumption

In the feed and water consumption, there was no significant difference between the treatment and control group (Figs. 3, 4, 5 and 6).

4. Urinalysis

The appearance and pH of the urine in the treatment groups were comparable to those in the control group and were within normal range of variation.

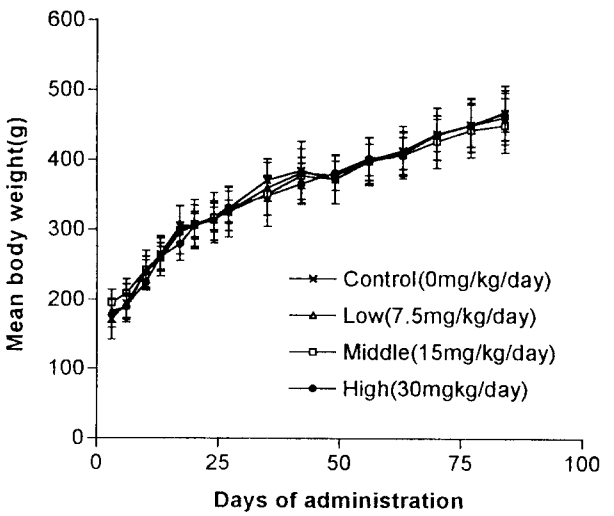

Fig. 1. Mean body weights in male rats intravenously injected with *Ginkgo biloba* extract(EGb 761). Each value represented the mean±SD of 10 rats.

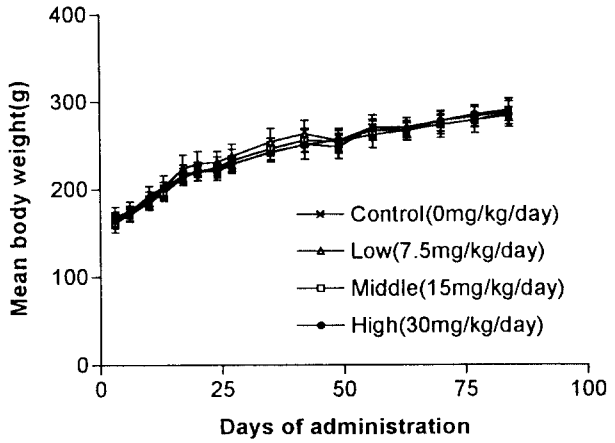

Fig. 2. Mean body weights in female rats intravenously injected with *Ginkgo biloba* extract (EGb 761). Each value represented the mean±SD of 10 rats.

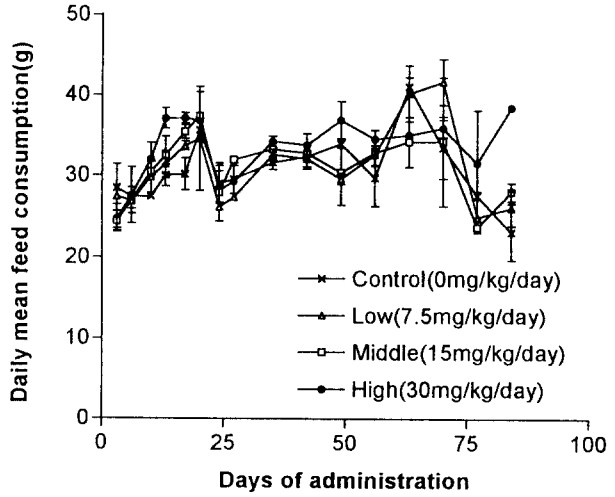

Fig. 3. Daily mean feed consumption in male rats intravenously injected with *Ginkgo biloba* extract(EGb 761). Each value represented the mean±SD of 10 rats.

5. Serum Biochemistry

Serum biochemical data are summarized in Table 1. There was a higher chloride (90.60±2.95) and creatinine (1.22±0.06) in males of low dosage group (7.5 mg/kg/day), while there was a lower alanine transaminase (ALT; 80.44±8.44) and potassium (8.28± 0.42) compared with control group. There was a higher creatinine (1.22±0.06) in males of middle dosage group (15 mg/kg/day), while there was a lower ALT (78.25±11.02) and cholesterol (93.20±9.64) compared with control group. There was a higher creatine (1.24±0.11) in males of high dosage group (30 mg/kg/day), while there was a lower cholesterol (90.50±

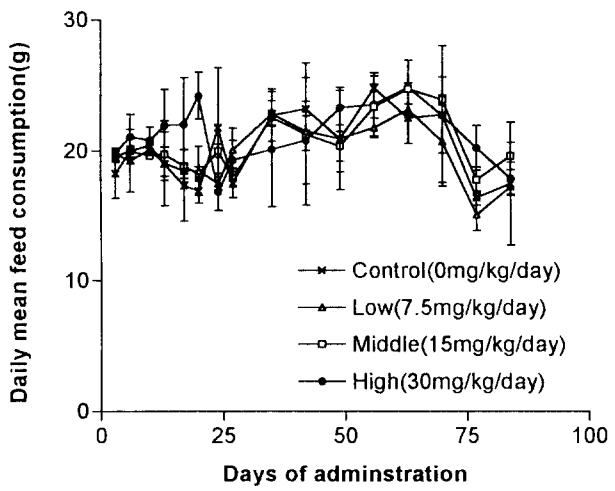

Fig. 4. Daily mean feed consumption in female rats intravenously injected with *Ginkgo biloba* extract(EGb 761). Each value represented the mean±SD of 10 rats.

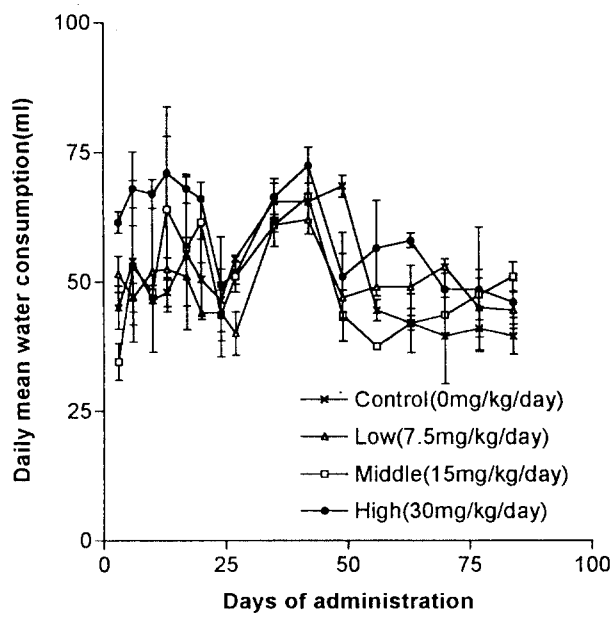

Fig. 5. Daily mean water consumption in male rats intravenously injected with *Ginkgo biloba* extract (EGb 761). Each value represented the mean±SD of 10 rats.

8.87) compared with control group.

There was a lower ALT (61.20±14.33) and alkaline phosphatase (71.70±19.01) in females of low dosage group (7.5 mg/kg/day) compared with control group. There was a lower ALT (64.10± 11.15), potassium (5.59±0.45), and albumin (3.17±0.37) in females of middle dosage group (15 mg/kg/day). There was a higher glucose (136.50± 23.42) and total protein (7.86±0.54) in females of

high dosage group (30 mg/kg/day), while there was a lower potassium (5.56±0.65) and albumin (3.32±0.42) compared with control group.

6. Hematology

Hematological data are summarized in Table 2.

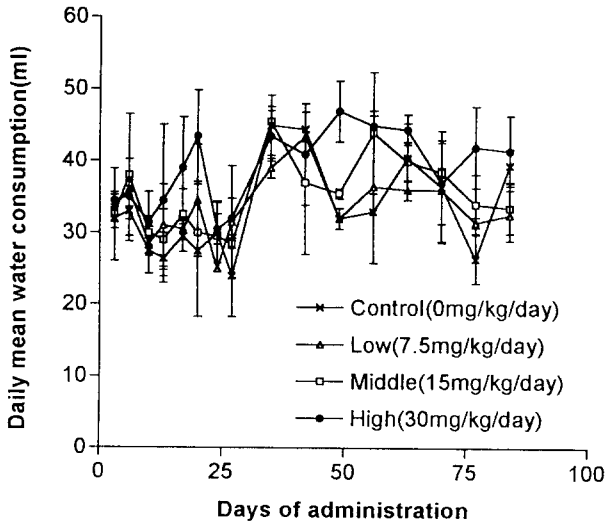

Fig. 6. Daily mean water consumption in female male rats intravenously injected with *Ginkgo biloba* extract(EGb 761). Each value represented the mean±SD of 10 rats.

There was a higher lymphocytes (12.93±4.44), basophil (0.07±0.04), leukocyte (1.46±0.81) counts in males of low dosage group (7.5 mg/kg/day), while there was a lower mean corpuscular hemoglobin (MCH; 13.6±0.42) compared with control group. There was a lower MCH (13.19±0.71) in males of middle dosage group (15 mg/kg/day) compared with control group. There was a lower MCH (13.13±0.58) and mean corpuscular hemoglobin concentration (MCHC; 26.10±0.92) in males of high dosage group (30 mg/kg/day) compared with control group.

There was a higher basophil (0.07±0.03) counts in females of low dosage group (7.5 mg/kg/day), while there was a lower mean corpuscular volume (MCV; 48.71±1.48) compared with control group. There were a higher hemoglobin (12.07±0.92), MCH (16.01±0.06), and MCHC (32.29±1.17) in females of middle dosage group (15 mg/kg/day), while there was a lower hematocrit (36.60±1.02) compared with control group. There was a higher hemoglobin (12.68±0.65), MCH (17.15±0.58), and MCHC (33.76±0.57) in females of high dosage group (30 mg/kg/day), while there was a lower hematocrit (37.53±1.77) compared with control

Table 1. Serum biochemical values of rats intravenously injected with *Ginkgo biloba* extract(EGb 761)

(Dose unit: mg/kg/day)

\Sex	Male				Female			
Parameter \Group	Control	Low	Middlie	High	Control	Low	Middlie	High
\Dose	0	7.5	15	30	0	7.5	15	30
\No. of animal	10	10	10	10	10	10	10	10
ALT (u/l)	95.00±11.62[a]	80.44± 8.44	78.25±11.02*	89.75±16.76	82.80±19.29	61.20±14.33*	64.10±11.15*	75.10±12.94
AST (u/l)	210.20±20.09	320.00± 9.20	315.90± 9.46	313.60±19.80	258.40±49.68	239.90±57.26	220.30±53.71	253.30±48.86
CHOL (mg/dl)	106.80±14.45	99.00± 8.27	93.20± 9.64*	90.50± 8.87*	89.60±10.05	83.70± 9.14	84.80± 9.98	97.60±19.20
GLU (mg/dl)	33.40±12.69	46.10±19.67	34.10±20.86	26.00±23.43	101.70±23.36	98.10±30.97	111.10±18.65	136.50±23.42*
TB (mg/dl)	0.50± 0.07	0.41± 0.03	0.47± 0.14	0.42± 0.18	0.48± 0.28	0.46± 0.13	0.45± 0.08	0.43± 0.07
TP (g/dl)	7.08± 0.44	7.34± 0.44	7.21± 0.34	7.19± 0.38	7.27± 0.44	7.54± 0.36	7.59± 0.60	7.86± 0.54*
TG (mg/dl)	86.70±24.28	69.40±10.49	77.60±30.96	74.20±23.32	66.40± 9.52	76.80±14.70	73.30±21.80	67.70±18.17
ALP (u/l)	170.80±42.16	168.90±85.37	190.10±67.81	168.60±66.88	100.10±34.74	71.70±19.01*	84.70±33.19	80.70±10.20
CL (meq/l)	94.20± 2.39	97.60± 2.95*	93.80± 2.74	91.90± 2.60	94.90± 3.03	94.00± 2.16	93.60± 4.90	97.60± 3.89
CREAT (mg/dl)	1.09± 0.09	1.22± 0.06*	1.23± 0.09*	1.24± 0.11*	0.94± 0.07	0.98± 0.06	0.93± 0.08	0.99± 0.09
BUN (mg/dl)	21.20± 4.61	20.10± 2.02	21.60± 2.37	23.40± 1.84	22.90± 4.04	20.20± 3.19	20.70± 4.57	20.10± 3.28
K (meq/l)	8.93± 0.53	8.29± 0.42*	9.26± 0.57	9.41± 0.93	6.32± 0.56	5.92± 0.53	5.59± 0.45*	5.56± 0.65*
Albumin (g/dl)	3.22± 0.23	3.07± 0.21	3.15± 0.16	3.18± 0.23	3.65± 0.28	3.39± 0.26	3.17± 0.37*	3.32± 0.42*

[a] Values were expressed mean±SD.

* significantly different from control group ($p < 0.05$).

ALT, alanine transaminase; AST, aspartate transaminase; CHOL, cholesterol; GLU, glucose; TB, total bilirubin; TP, total protein; TG, triglyceride; ALP, alkaline phosphatase; CL, chloride; CREAT, creatinine; BUN, blood urea nitrogen.

group.

7. Coagulation

Coagulative data are summarized in Table 3. There was no significant different prothrombin time (PT) and partial thromboplastin time (PTT) between treatment and control group.

8. Relative Organ Weights

Relative organ data are summarized in Table 4. There was a higher adrenal gland weight of males of low dosage group (7.5 mg/kg/day). There was a higher liver and spleen weights of males of high dosage group (30 mg/kg/day) compared with control group.

There was a higher spleen weight of females of low dosage group (7.5 mg/kg/day) while there was a lower liver weights compared with control group. There was a higher spleen and heart of females of high dosage group (30 mg/kg/day) while there was a lower liver weight compared with control group.

9. Histopathology

There was a hemosiderosis in the spleen of

Table 2. Hematological values of male rats intravenously injected with *Ginkgo biloba* extract (EGb 761)

(Dose unit: mg/kg/day)

\Sex	Male				Female			
Parameter \Group	Control	Low	Middlie	High	Control	Low	Middlie	High
\Dose	0	7.5	15	30	0	7.5	15	30
\No. of animal	10	10	10	10	10	10	10	10
Neutrophil ($\times 10^3/\mu l$)	1.45± 0.40[a]	2.42± 2.32	1.43± 0.50	1.19± 0.89	0.98± 0.80	1.84± 1.62	0.97± 0.62	0.97± 0.62
Lymphocyte ($\times 10^3/\mu l$)	9.18± 2.02	12.93± 4.44*	10.52± 3.30	10.56± 1.11	8.85± 4.05	8.80± 7.03	9.66± 3.98	9.66± 3.98
Monocyte ($\times 10^3/\mu l$)	0.24± 0.21	0.44± 0.64	0.18± 0.05	0.30± 0.21	0.55± 0.58	1.04± 1.06	0.36± 0.30	0.36± 0.30
Eosinophil ($\times 10^3/\mu l$)	0.20± 0.07	0.22± 0.16	0.13± 0.08	0.10± 0.09	0.14± 0.13	0.57± 1.04	0.13± 0.07	0.13± 0.07
Basophil ($\times 10^3/\mu l$)	0.03± 0.02	0.07± 0.04*	0.04± 0.02	0.05± 0.01	0.04± 0.03	0.07± 0.03*	0.05± 0.01	0.05± 0.01
Leucocyte ($\times 10^3/\mu l$)	0.71± 0.16	1.46± 0.81*	0.75± 0.22	1.05± 0.82	0.73± 0.54	1.55± 1.58	0.94± 0.80	0.94± 0.80
WBC ($\times 10^3/\mu l$)	11.84± 2.38	15.53± 5.93	13.05± 3.57	12.09± 1.88	11.28± 3.73	12.78± 3.77	11.90± 3.24	11.90± 3.24
RBC ($\times 10^3/\mu l$)	8.49± 0.30	8.32± 0.41	7.98± 2.36	8.37± 0.64	7.63± 0.36	7.90± 0.20	7.50± 0.37	7.50± 0.37
HGB (g/dl)	11.81± 1.24	10.86± 0.61	10.62± 3.21	10.87± 0.67	9.63± 1.12	10.50± 1.93	12.07± 0.92*	12.07± 0.92*
HCT (%)	21.23± 1.71	40.14± 2.06	39.24± 11.78	41.35± 2.11	39.22± 1.89	38.27± 1.17	36.60± 1.02*	36.60± 1.02*
MCV (fL)	49.80± 0.97	48.26± 1.52	49.03± 1.86	50.56± 2.11	51.47± 1.67	48.71± 1.48*	50.03± 1.79	50.03± 1.79
MCH (pg)	13.89± 1.16	13.06± 0.42*	13.19± 0.71*	13.13± 0.58*	12.68± 1.86	13.38± 2.58	16.01± 0.66*	16.01± 0.66*
MCHC (g/dl)	27.91± 1.97	27.07± 0.67	26.93± 0.85	26.10± 0.92*	24.60± 3.30	27.41± 5.34	32.29± 1.17*	32.29± 1.17*
PLT ($\times 10^3/\mu l$)	878.80±99.73	767.60±163.84	803.80±243.40	888.50±210.56	825.70±134.36	914.60±113.20	884.00±127.35	884.00±127.35

[a] Values were expressed as mean±S.D.

* significantly different from control group ($p < 0.05$).

WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corposcular hemoglobin; MCHC, mean corposcular hemoglobin concentration; PLT, platelet.

Table 3. Prothrombin time and thromboplastin time of male and female rats intravenously injected with *Ginkgo biloba* extract(EGb 761)

(unit: second)

Sex		\Group \Dose (mg/kg/day) \No. of animal	Control 0 3	Low 7.5 3	Middle 15 3	High 30 3
Male	PT	Mean	12.20	12.00	12.10	13.00
		S.D.	1.81	1.83	1.91	1.33
	PTT	Mean	24.70	24.40	23.70	24.20
		S.D.	2.79	3.06	2.75	2.74
Female	PT	Mean	11.40	10.90	11.80	11.20
		S.D.	1.84	1.45	1.40	1.93
	PT	Mean	24.50	24.30	24.30	24.40
		S.D.	2.01	1.83	1.49	1.84

Table 4. Relative organ weights of male rats intravenously injected with *Ginkgo biloba* extract(EGb 761) (unit: %)

Parameter \Sex	Male				Female			
\Group	Control	Low	Middlie	High	Control	Low	Middlie	High
\Dose	0	7.5	15	30	0	7.5	15	30
\No. of animal	10	10	10	10	10	10	10	10
Liver	2.99[b]±0.22	3.04±0.18	3.19±0.19*	2.94±0.16	3.15±0.18	2.86±0.23*	3.01±0.32	2.90±0.21*
Spleen	0.17 ±0.04	0.32±0.11*	0.31±0.04*	0.23±0.04	0.23±0.04	0.34±0.06*	0.33±0.06*	0.28±0.04*
Kidney left	0.34 ±0.03	0.35±0.03	0.35±0.03	0.35±0.02	0.38±0.03	0.36±0.02	0.37±0.03	0.34±0.04
Kidney right	0.35 ±0.04	0.35±0.02	0.36±0.03	0.37±0.03	0.37±0.02	0.37±0.02	0.36±0.02	0.36±0.03
Adrenal [c]gl. left	0.01 ±0.00	0.01±0.00	0.01±0.00	0.01±0.00	0.02±0.01	0.02±0.00	0.02±0.00	0.02±0.00
Adrenal gl. right	0.01 ±0.00	0.01±0.00	0.01±0.00	0.01±0.00	0.02±0.00	0.01±0.00	0.02±0.00	0.02±0.01
Heart	0.31 ±0.04	0.31±0.02	0.31±0.03	0.32±0.03	0.34±0.03	0.34±0.03	0.34±0.02	0.37±0.04*
Lung	0.56 ±0.11	0.54±0.08	0.56±0.08	0.58±0.11	0.66±0.09	0.64±0.09	0.57±0.12	0.72±0.13
Salivary gl. left	0.10 ±0.02	0.11±0.03	0.10±0.02	0.09±0.02	0.10±0.01	0.11±0.04	0.11±0.03	0.11±0.02
Salivary gl. right	0.09 ±0.03	0.09±0.02	0.11±0.02	0.10±0.03	0.09±0.01	0.10±0.02	0.10±0.03	0.10±0.03
Brain	0.46 ±0.03	0.45±0.03	0.47±0.03	0.47±0.04	0.70±0.03	0.69±0.04	0.70±0.04	0.70±0.06
Testis left	0.34 ±0.04	0.32±0.08	0.36±0.06	0.36±0.03	0.03±0.01	0.03±0.01	0.03±0.01	0.03±0.01
Testis right	0.33 ±0.03	0.32±0.08	0.37±0.04	0.36±0.03	0.03±0.01	0.03±0.01	0.03±0.01	0.03±0.01

[a] Dose unit was mg/kg/day; [b] Values were expressed as mean±SD.; [c] gl., gland; * significantly different from control group ($p < 0.05$).

males of high dosage group (30 mg/kg/day). Large numbers of macrophages were infiltrated into the white pulp. Occasionally, macrophages have vacuoles in the cytoplasm. Glycogen accumulations were seen in the hepatocytes around central vein in males of high dosage group (30 mg/kg/day). Lymphocytolysis and apoptotic body were seen in the white pulp of spleen in females of high dosage group (30 mg/kg/day). Splenic hemosiderosis and hepatic glycogen accumulation were also seen in other treatment groups in both male and female and control group. No other histopathological lesions were seen in treatment and control group.

IV. DISCUSSION

Ginkgo biloba extract plays a important role as a strong vasoregulatory factor and a treatment of brain dysfunction and peripheral arterial disease such as difficulties of memory, dizziness, tinnitus, headache and emotional instability with anxiety (Semlitsch H. V., *et al.*, 1995).

The present reports describe findings in rat injecting intravenously *Ginkgo biloba* extract(EGb 761) with various dosages such as 7.5 mg/kg/day (low dosage group), 15 mg/kg/day (middle dosage group), or 30 mg/kg/day (high dosage group) for 3 month by tail vein according to Established Regulation of Korean National Institute of Safety Research (1994. 4. 14). No laboratory animals in treatment and control group were dead. In male *Ginkgo biloba* extract(EGb 761)-treated groups, *Ginkgo biloba* extract(EGb 761) may alter number of lymphocytes. *Ginkgo biloba* extract(EGb 761) injected in high concentrations may decrease MCH and MCHC. In female *Ginkgo biloba* extract(EGb 761)-treated groups, *Ginkgo biloba* extract(EGb 761) may alter number of basophils. *Ginkgo biloba* extract(EGb 761) injected in high concentrations may decrease hemoglobin, hematocrit, MCV, MCH, and MCHC. In male *Ginkgo biloba* extract(EGb 761)-treated groups, *Ginkgo biloba* extract(EGb 761) injected in high concentrations may increase creatinine and cholesterol. In female *Ginkgo biloba* extract(EGb 761)-treated groups, *Ginkgo biloba* extract(EGb 761) injected in high concentrations may increase potassium and albumin. In male and female *Ginkgo biloba* extract(EGb 761)-treated groups, *Ginkgo biloba* extract(EGb 761) may alter ALT, glucose, total protein, and ALP. Although some hematological and serum biochemical data may be statistically significant, these alterations may be not directly due to *Ginkgo biloba* extract (EGb 761) on the basis of clinical signs and histopathological observation.

Although relative organ weight of spleen and liv-

er is significantly higher in the treatment group than in the control groups, weight difference may be not due to *Ginkgo biloba* extract(EGb 761) but due to degree of exsangunation at autopsy or other unknown factors. In addition, no significant differences were not observed in urinalysis, PT, and PTT in both treatment and control group.

Male in *Ginkgo biloba* extract(EGb 761)-treated and control groups had hemosiderosis and infiltration of macrophages, and lipid-laden macrophages in the spleen and glycogen degeneration in the liver. Female in *Ginkgo biloba* extract(EGb 761)-treated and control groups had lymphocytolysis, increased apoptotic bodies, centrolobular glycogen accumulation Since these histopathological lesions were seen in most of treatment and control groups, these pathological alterations have not beed due to *Ginkgo biloba* extract(EGb 761). DeFeudis *et al.* also reported that Ginkgo biloba extract tested into patients clinically and found a mild adverse effects such as gastrointestinal compliant, headache, and skin allergin skin reaction (DeFeudis F. G. *et al.*, 1991). Our data and other study (DeFeudis F. G. *et al.*, 1991) suggested that *Ginkgo biloba* extract(EGb 761) should be nontoxic.

In conclusion, the intravenous administration of *Ginkgo biloba* extract(EGb 761) in rats for 3 month showed no clinical signs and histopathological lesions. Therefore, *Ginkgo biloba* extract(EGb 761) could be nontoxic for subacute toxicity study.

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