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Fertility and General Reproductive Ability Test of *Ginkgo Biloba* Extract (EGb 761) in Rats

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ABSTRACT : *A fertility and general reproductive ability study was performed in Sparque-Dawley rats intravenously injected with Ginkgo biloba extract (EGb 761), a potential pharmaceutical excipient, at dose levels of 7.5, 15, and 30 mg/kg/day. Male rats were treated with Ginkgo biloba extract (EGb 761) from 14 days before mating until 21 days after delivery. Female rats received extract for 2 months prior to mating. No abnormal signs were noted in mating or fertility of the rats treated with Ginkgo biloba extract (EGb 761). No significant external, visceral, and skeletal anomalies or mental and physical development attributable to treatment was noted in any fetuses examined. The fertility of F1 generation was not affected by the treatment also. It was concluded that Ginkgo biloba extract (EGb 761) has no harmful effect on mating, fertilization, implantation, embryonic development and normal physical development.*

Key Words : *Ginkgo biloba extract (EGb 761), Fertility and general reproductive ability test, Rats*

I. INTRODUCTION

Ginkgo biloba extract has strong pharmacological effect in vascular physiology. As a strong antagonist of platelet activating factor, *Ginkgo biloba* extract can increase microvascular permeability, bronchoconstriction, and vasoregulatory activity of blood vessels. Therefore *Ginkgo biola* extract might be a good model compound to develop as a new therapeutic agent for curing humans circulatory disorders (Jos K *et al.*, 1992). Recently, *Gingko biola* extract has also been used for treating several central nervous system dysfunctions such as headache, dizziness, and memory loss (Jos K. *et al.*, 1992, Schneider B., 1992, and Semlitsch, H.V. *et al.*, 1995).

This study was performed to examine the fertility and general reproductive ability of *Ginkgo biloba* extract (EGb 761) which was purified and provided by YuYu Inc.

II. MATERIALS AND METHODS

1. Chemical

Ginkgo biloba extract (EGb 761) was provived by YuYu, Inc. *Ginkgo biloba* extract (EGb 761) was dissolved in citrate buffer solution before use.

2. Animals and Treatment

Male and female Sprague-Dawley rats were obtained from Seoul National University Laboratory Animal Center and allowed to acclimate for 2 weeks before use. Rats were given commercial laboratory chow and water and were maintained on a 12-hour light and dark cycle. Nine month old female and 5-month-old male rats were randomly assigned and dosed with 7.5 mg/kg/day (Low group), 15 mg/kg/day (Middle group), and 30 mg/kg/day (High group) of extract or with vehicle only (Control group). In male rats, the rats were treated with test chemical for 2 months. In female rats, the treatment was initated 14 days before mating and contiuned until day 21 after delievery. During mating period, the female rats were paired at 1 : 1 basis with the male rats.

3. Effect of *Ginkgo Biloba* Extract (EGb 761) on F0 Generation

Body weight and food consumption and water intake of male rats were monitored every week from week 0 to week 11. In female rats, body weight and food consumption and water intake were monitored day 1, 3, 5, 7, 9, 14, and 20 of pregnancy and 1, 4, 12, and 21 days after delivery. Female and male rats were mated 1 : 1 ratio and mating was confirmed by the presence of sperm and corpulation plug in vaginal smear. The day when mating was confirmed was regarded as day 0 of pregnancy.

Male rats were necropsized one day after mating. Half of pregnant female rats were killed by cardiac punture under ether anesthesia and careful gross examination, placental weight, and pregnancy index was measured. The rest of pregnant female rats were used to check fetal death and the number of corpus luteum and implantation. Teratological examination of fetuses were performed.

4. Effect of *Ginkgo Extract* on F1

Mental and physical development of the fetuses was monitored. The physical developmental status was examined based on the degree of pinna detachment, incisor eruption, eyelid opening, testicular descent, and vaginal opening. Reflex test was based on pina response, surface righting reflex, cliff version, negative geotaxis, pupillary reflex, and auditory test. Female and male rats of F1 generation were mated and copulation rate, the ratio of fertility, implantion rate, fetal sex ratio, and the number of fetuses were examined one day before delivery after Caesarean section.

5. Effect of *Ginkgo Extract* on F1

Mental and physical development of the fetuses was monitered. The physical developmental status was examined based on the degree of pinna detachment, incisor eruption, eyelid opening, testicular descent, and vaginal opening. Reflex test was based on pina response, surface righting reflex, cliff version, negative geotaxis, pupillary reflex, and auditory test.

6. Statistical Analysis

The resutls were statistically analyzed by Dunnett's t-test and non-parametric one way Kruskal-Wallis test.

III. RESULTS

1. Effect of *Ginkgo Extract* on F0

1) Effect on Body Weight Change and Food Consumption and Water Intake

No significant difference of body weight change between treated and control groups was found

Table 1. Mean body weight of female rats (F0) intravenously injected with *Ginkgo biloba* extract (unit: gm)

	Group Dose (mg/kg/day)	Control 0	Low 7.5	middle 15	High 30
	No. of animal	20	20	20	20
Before mating (week)	0	269.62±23.78[a]	269.09±19.76	277.53±26.66	262.76±29.72
	1	270.18±24.69	266.62±23.82	270.2 ±27.65	273.62±26.05
	No. of animal	18	17	16	20
During pregnancy (day)	1	277.83±23.07	273.04±17.70	291.86±25.24	287.26±28.73
	3	285.49±22.62	278.99±19.70	298.26±29.74	294.95±27.86
	5	290.71±23.68	285.39±18.58	302.10±30.29	300.23±29.34
	7	294.28±23.13	288.15±19.50	307.36±30.64	302.88±29.62
	14	323.52±30.55	312.85±25.48	329.78±37.15	334.39±30.89
	20	392.96±31.69	386.24±34.92	403.55±50.30	413.79±36.36
	No. of animal	10	7	9	10
After arturition (day)	1	304.32±21.00	317.14±15.33	332.69±35.84	314.03±27.07
	4	303.41±21.72	311.40±19.09	318.96±24.30	320.03±27.48
	12	323.02±18.00	322.94±18.61	342.42±29.04	337.65±24.17
	21	327.27±18.01	330.37±21.85	337.37±20.40	332.84±23.92

[a] Mean±S.D.

(Tables 1 and 2). In female rates, food consumption of high group measured one week before mating and middle group measured 12 days after delivery were significantly increased compared to that of control group. Water intake of female rats was signifcantly increased in all three treated groups when measured day 20 of pregnancy (Tables 3 and 4). There was no statistically signifcant difference of food consumption and water intake between treated and control group of male rats (Tables 5 and 6).

2) Effect on Copulation Rate

Copulation rate was 100% regardless of the treatment (Tables 7).

3) Effect on the Ratio of Fertility

The ratio of fertility was 90% in Control group. In treated group, the ratio of Low, Middle and High group were 85%, 80% and 100%, respectively. Therefore no significant statistical difference was noted between treated and control groups (Table 7).

4) Effect on Pregnancy Index of Pregnant Female Rats

No significant statistical difference was found between treated and control rats (Table 8).

Table 2. Mean body weight of male rats (F0) intravenously injected with *Ginkgo biloba* extract (unit: gm)

Week	Group Dose (mg/kg/day) No. of animal	Control 0 20	Low 7.5 20	Middle 15 20	High 30 20
0		218.24±54.33[a]	223.45±53.51	213.46±43.15	237.67±38.69
1		286.14±53.06	297.55±55.91	286.13±45.01	288.42±39.16
2		321.23±52.19	335.40±55.40	313.95±40.91	324.71±36.68
3		360.62±54.84	382.75±58.39	371.17±40.74	384.55±41.52
4		350.95±54.68	372.22±55.77	363.32±38.19	358.32±38.03
5		354.15±56.24	377.35±50.31	365.96±37.10	362.07±37.65
6		364.28±57.75	383.67±51.24	380.70±37.25	381.02±36.11
7		400.12±67.61	426.77±53.91	421.14±39.47	420.18±36.22
8		434.56±62.50	435.20±57.85	434.06±41.03	448.30±36.17
9		443.56±69.19	464.32±57.41	447.48±40.06	449.81±39.93
10		462.56±69.19	480.01±59.90	462.38±41.74	471.58±40.69
11		474.04±66.03	488.98±58.80	474.37±38.88	480.76±42.08

[a]Mean±S.D.

Table 3. Mean feed consumption of female rats (F00 intravenously injected with *Ginkgo biloba* extract (unit: gm)

	Group Dose (mg/kg/day)	Control 0	Low 7.5	Middle 15	High 30
	No. of animal	20	20	20	20
Before mating (week)	0	12.71±7.63[a]	11.71±5.31	12.59±4.65	13.37±5.22
	1	13.97±2.34	14.63±3.76	15.16±2.35	17.44±5.35*
	No. of animal	18	17	16	20
During pregnancy (day)	1	21.54±7.70	18.66±1.57	19.81±2.24	21.18±3.35
	3	21.71±4.43	22.14±3.86	22.57±3.66	21.77±3.15
	5	21.46±4.46	23.45±2.98	24.22±4.32	23.40±3.69
	7	22.13±5.24	23.09±5.51	22.53±4.23	24.84±4.22
	14	32.24±4.24	31.18±5.40	34.65±3.90	34.63±5.09
	20	28.29±3.81	32.62±6.58	31.81±8.68	32.73±6.57
	No. of animal	10	7	9	10
After parturition (day)	1	19.93± 7.29	26.47±18.08	25.03± 6.30	21.82±10.13
	4	32.76±10.01	36.40±11.36	39.13± 8.59	38.70± 6.02
	12	53.35± 7.31	50.99± 9.01	65.48± 8.75*	58.92±12.15
	21	77.44±21.95	88.90±12.63	9.136±22.02	96.67±19.04

[a]Mean±S.D.

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

Table 4. Mean water consumption of female rats (F0) intravenously injected with *Ginkgo biloba* extract (unit: gm)

	Group Dose (mg/kg/day)	Control 0	Low 7.5	Middle 15	High 30
	No. of animal	20	20	20	20
Before mating (week)	0	34.75±10.70[a]	36.50± 9.61	34.50±10.50	34.25±11.73
	1	36.50±11.82	38.50±10.53	36.50±11.37	34.75±13.33
	No. of animal	18	17	16	20
During pregnancy (day)	1	36.39± 5.37	37.35±16.12	38.44±17.86	41.00± 7.71
	3	36.94± 7.69	42.94±16.96	38.75±11.90	44.00±13.04
	5	37.22± 6.91	39.12± 6.67	40.31± 6.94	38.50±11.25
	7	38.89± 8.14	39.12± 7.95	37.81± 8.16	41.50±10.40
	14	64.17±12.16	57.35±14.70	60.63±11.09	65.00±11.24
	20	76.94±15.64	59.12±16.61*	63.13±17.02*	63.75±17.00*
	No. of animal	10	7	9	10
After parturition (day)	1	48.50±20.82	60.71±15.12	47.78±7.55	50.50±16.74
	4	69.00±10.49	65.71±10.58	71.11±10.83	79.50±11.17
	12	97.00±13.78	86.43±20.15	117.78±22.93	117.50±22.64
	21	136.00±30.44	140.71±50.86	152.78±17.87	164.00±21.83

[a], Mean±S.D.
*, significantly different from contrl group ($p < 0.05$).

Table 5. Mean feed consumption of male rats (F0) intravenously injected with *Ginkgo biloba* extract (unit: gm)

Week	Group Dose (mg/kg/day) No. of animal	Control 0 20	Low 7.5 20	Middle 15 20	High 30 20
0		14.83± 8.19[a]	13.01± 5.95	14.33± 5.02	14.67± 5.41
1		13.17± 6.67	15.83±14.02	12.50±15.71	14.58± 7.87
2		15.50±13.62	14.67±12.46	14.71±12.62	13.92± 7.04
3		16.71±17.31	17.13± 9.43	16.21±10.11	17.07± 9.63
4		19.43± 9.76	16.37±10.17	17.36± 9.87	16.97±10.42
5		20.17± 9.43	19.44±11.17	19.57±10.37	19.76±10.43
6		22.46± 9.18	21.36±10.24	22.57± 9.39	23.41± 9.73
7		21.36±10.44	22.18±10.76	23.48±10.18	24.16± 9.79
8		23.77± 9.47	24.16±10.11	25.78± 9.76	26.43±10.26
9		24.84±10.43	26.17± 9.36	27.14±10.64	28.31± 9.78
10		25.14± 9.79	27.89± 9.96	26.43±10.89	29.41±10.46
11		24.31±10.47	26.49± 9.74	25.39± 8.49	28.79± 9.47

[a]Mean±S.D.

Table 6. Mean water consumption of male rats (F0) intravenously injected with *Ginkgo biloba* extract (unit: gm)

Week	Group Dose (mg/kg/day) No. of animal	Control 0 20	Low 7.5 20	Middle 15 20	High 30 20
0		33.74± 9.14[a]	25.89± 8.34	24.36± 7.61	30.67± 9.68
1		34.63± 8.17	27.33± 9.18	28.83± 8.14	32.84± 9.91
2		35.18± 9.16	29.41±10.11	29.97± 9.77	31.19±10.45
3		36.91± 9.77	34.51± 9.31	30.14± 9.19	33.31± 9.16
4		37.41± 8.89	35.65± 9.17	31.18± 8.17	34.16±10.13
5		37.79±10.11	37.24± 9.91	33.47± 9.19	36.87±10.94
6		39.41± 9.45	39.47±10.17	36.24±10.73	38.16± 9.47
7		41.32±10.39	42.73± 9.87	40.92± 9.51	41.18±10.15
8		43.91± 8.97	45.54±10.93	43.87± 9.77	42.83±10.13
9		45.16±10.17	47.68±11.76	46.97±10.89	47.31±12.19
10		47.84±11.99	49.84±10.91	48.91±11.78	50.71±13.41
11.		44.71±10.11	45.76± 9.76	46.71± 9.56	45.13±12.11

[a]Mean±S.D.

Table 7. Reproductive ability of male/female (F0) rats intravenously injected with *Ginkgo biloba* extract

		Control (0 mg/kg/day)	Low (7.5 mg/kg/day)	Middle (15 mg/kg/day)	High (30 mg/kg/day)
No. of animal	\Male	20	20	20	20
for mating	\Female	20	20	20	20
No. of	\Male	20	20	20	20
corpulated	\Female	20	20	20	20
animal		18	17	16	20
No. pregnant	\Male	100	100	100	100
animal	\Female	100	100	100	100
Corpulation		90	90	80	100

[a](Number of mating animal/total number of animal)× 100.
[b](Number of pregnant animal/number of mating animal)× 100.

Table 8. Pregnancy index of female rats (F0) intravenously injected with *Ginkgo biloba* extract

		Control	Low	Middle	High
No. pregnant animal		18	17	16	20
Corpus Luteum		18.9± 3.9[a]	19.1± 5.5	19.4± 6.1	19.3± 3.1
Implantation		12.1± 4.4	10.7± 5.0	11.0± 6.4	14.3± 2.5
Litter size	\Male	5.9± 2.1	6.3± 2.4	6.6± 2.9	6.2± 2.3
	\Female	6.8± 2.0	4.9± 2.6	6.4± 2.4	7.7± 2.5
Dead fetus ratio[b]	\Early	0	0	0	0
	\Late	0	0	0	0
Implantation ratio[c]		71.4±10.7	64.6±14.1	64.2±20.9	73.3±11.3
Resorption ratio[d]		4.2± 5.3	10.1±23.5	7.4±16.2	3.0± 5.5
Death ratio after birth[e]		6.5±13.2	32.3±39.5	0.0± 0.0	0.8± 2.5
Sex ratio[f]		1.3± 2.0	1.8± 1.8	1.2± 0.9	0.9± 0.5
Placental weight	\Left	0.8± 0.1	0.8± 0.1	0.8± 0.2	0.8± 0.2
	\Right	0.8± 0.1	0.7± 0.1	0.8± 0.2	0.8± 0.2

[a]Mean±S.D.
[b](Number of dead fetus/number of implantation)× 100.
[c](Number of implantion/number of corpus luteum)× 100.
[d](Number of fetus absorbed/number of implantion)× 100.
[e](Number of dead pups after birth/number of total pups)× 100.
[f]Number of male/number of female.

Table 9. Effect of *Ginkgo biloba* extact on exteral malformation in rat fetus (F1)

Group Dose (mg/kg/day)	Control 0	Low 7.5	Middle 15	High 30
No. of dams	8	10	7	10
No. of examined fetuses	106	125	82	140
Fused placenta	0	0	0	0
Hematoma	0	0	0	0
Hemorrhage in the Yolk-Sac	0	0	0	0
Exencephaly	0	0	0	0
Exophthalmia	0	0	0	0
Annurysm	0	0	0	0
Dislocation of ear	0	0	0	0
Abnormal face	0	0	0	0
Hind limb ab.	0	0	0	0
Kinky tail	0	0	0	0
External malformaltion (%)[a]	0	0	0	0

[a](No. of abnormal fetus/no. of examined fetus)× 100.

Table 10. Effect of *Ginkgo biloba* extact on visceral malformation of rat fetus (F1)

Group Dose (mg/kg/day)	Control 0	Low 7.5	Middle 15	High 30
No. of dams	8	10	7	10
No. of examined fetuses	106	125	82	140
Aberrant right subclavian art.	0	0	0	0
Esophagus tracheal constriction	0	0	0	0
Ventricular septal defect	0	0	0	0
Dilatation of renal pelvis	0	0	0	0
Renal displacement	0	0	0	0
Dilatation of subarachnoid space	0	0	0	0
Visceral malformaltion (%)[a]	0	0	0	0

[a](No. of abnormal fetus/no. of examined fetus)× 100.

5) Effect on Fetuses

Fetal sex ratio was not significantly different (Table 8) between treated and control rats. No significant external, visceral or skeletal malformations were observed in fetuses from rats (Tables 9, 10, and 11). However, fetal body weight of rats from Control group was significantly lower than those from Low and Middle group (Table 12).

2. Effect of *Ginkgo Biloba* Extract (EGb 761) on F1 Generation

1) Effect on Fetal Sex Ratio, Body Weight and Number of Fetus

Fetal death ratio and fetal sex ratio were not statistically different between treated and control groups (Table 8). There is statistically difference of the body weight between F1 male and female rats (Tables 13 and 14).

2) Effect on Mental and Physical Development of F1

Table 11. Effect of *Ginkgo biloba* extact on skeletal malformation of rat fetus (F1)

Group Dose (mg/kg/day)	Control 0	Low 7.5	Middle 15	High 30
No. of dams	8	10	7	10
No. of examined fetuses	106	125	82	140
Mandibular hypoplasia	0	0	0	0
Parietal hypoplasia	0	0	0	0
Interparietal bone hypoplasia	0	0	0	0
Forelimb ectrodactyl	0	0	0	0
External malformaltion (%)[a]	0	0	0	0

[a](No. of abnormal fetus/no. of examined fetus)×100.

Table 12. F1 fetal body weight at Caesarean section

Group Dose (mg/kg/day) 106	Control 0 106	Low 7.5 125	Middle 15 82	High 30 139
Body weight (mean±S.D.)	4.12 ±0.61	3.86 ±0.43*	4.02 ±0.61	3.89 ±0.61*

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

Table 13. Body weight of F1 male rats after birth (unit: g)

Day after birth	Group Dose (mg/kg/day) Control 0	Low 7.5	Middle 15	High 30
0	5.93± 1.26[a]	6.43± 0.86	6.84±0.88*	6.57±0.64*
1	7.19± 0.72	7.71± 0.94*	7.55±0.90	7.25±0.74
2	7.79± 0.89	8.35± 1.53	8.51±0.88*	8.22±0.66
3	8.58± 2.19	9.99± 1.85*	9.85±1.01*	9.46±0.70
4	10.62± 1.39	11.51± 2.55*	11.45±1.23*	11.05±0.87
5	12.38± 1.94	13.21± 2.87	13.32±1.50	12.88±0.96
10	22.85± 3.49	22.55± 5.83	24.01±2.64	23.11±2.01
18	37.95± 5.66	40.86± 8.37*	39.83±3.36*	39.06±2.85
24	54.25±10.33	59.58±12.49	59.35±8.09	59.17±6.30

[a]Mean±S.D.
* significantly different from control group ($p < 0.05$).

Table 14. Body weight of F1 female rats after birth (unit: g)

Day after birth	Group Dose (mg/kg/day) Control 0	Low 7.5	Middle 15	High 30
0	5.91±0.75[a]	6.40±0.89*	6.58±0.82*	6.50±0.56*
1	6.82±0.78	7.24±0.96	7.30±1.02	7.03±0.54
2	7.50±0.92	7.79±1.52	8.12±1.02	7.97±0.55
3	8.80±1.41	9.32±2.10*	9.55±1.24	9.34±0.59
4	10.14±1.72	11.45±2.14*	11.01±1.33*	10.90±0.95
5	11.95±2.39	13.26±2.00	12.89±1.62	12.80±1.08
10	21.57±4.09	23.03±4.11	22.96±2.83	22.58±2.27
18	35.77±6.18	38.99±5.91	38.15±3.46	38.24±3.62
24	51.79±8.83	57.76±8.80*	55.26±7.63	56.71±6.22*

[a]Mean±S.D.
* significantly different from control group ($p < 0.05$).

Table 15. Reflex test of F1 rats

Sex	Group	Pinna response (7 day)		Surface righting reflex (9 day)	Cliff aversion (11 day)	Negative geotaxis (14 day)	Pupillary reflex (21 day)		Auditory test (35 day)
		Right	Left				Right	Left	
Male	Control	1/35[a]	0/35	0/35	0/35	0/35	0/35	0/35	0/35
	Low	0/19	1/19	1/19	1/19	0/18	0/18	0/18	0/18
	Middle	2/35	0/35	0/35	0/35	0/35	0/35	0/35	0/35
	High	2/39	0/39	1/38	1/38	0/38	0/38	0/38	0/38
Female	Control	2/33	0/33	0/33	0/33	0/33	0/33	0/33	0/33
	Low	0/14	2/14	0/13	0/13	0/13	0/13	0/13	0/13
	Middle	1/35	0/35	0/35	0/35	2/35	0/35	0/35	0/35
	High	1/38	1/38	0/38	2/38	0/38	0/38	0/38	0/38
Total	Control	3/68	0/68	0/68	0/68	0/68	0/68	0/68	0/68
	Low	0/33	3/33	1/32	1/32	1/32	0/32	0/32	0/32
	Middle	3/70	0/70	0/70	0/70	3/70	0/70	0/70	0/70
	High	3/77	1/77	0/76	3/76	0/76	0/76	0/76	0/76

[a]Number of abnormally developed F1/number of total F1.

Table 16. Physical development of F1 rats

Sex	Group	Pinna detachment (4 day)		Incisor eruption (14 day)	Eyelid opening (18 day)	Testicular descent (28 day)	Vagina opening (35 day)
		Right	Left				
Male	Control	0/35[a]	0/35	0/35	0/35	0/35	0/35
	Low	1/20	1/20	1/19	0/18	0/18	0/18
	Middle	0/35	0/35	0/35	1/35	0/35	0/35
	High	1/39	0/39	0/38	0/38	0/38	0/38
Female	Control	2/35	1/35	0/33	0/33	0/33	0/33
	Low	0/16	0/16	0/14	0/14	0/14	0/14
	Middle	0/35	0/35	0/35	0/35	0/35	0/35
	High	0/38	0/38	0/38	0/38	0/38	0/38
Total	Control	2/70	3/70	0/68	0/68	0/68	0/68
	Low	1/36	1/36	0/33	0/33	0/33	0/33
	Middle	0/70	0/70	1/70	0/70	0/70	0/70
	High	1/77	0/77	0/77	0/77	0/77	0/77

[a]Number of abnormally developed F1/number of total F1.

Table 17. Reproductive ability of f1 rats

	Control	Low	Middle	High
No. of pairs mated	33	14	35	38
No. of pairs corpulated	33	14	35	38
No. pregnant animal	30	13	33	35
Corpulation ratio (%)[a]	100	100	100	100
Fertility ratio (%)[b]	90	92	94	92

[a](Number of mating animal/total number of animal)× 100.
[b](Number of pregnant animal/number of mating animal)× 100.

Reflex test and physical development were normal regarless of the treatment (Tables 15 and 16).

3) Fertility of F1

No statistical difference of reproductive ability and pregnancy index was noted between treated and control rats (Tables 17 and 18).

IV. DISCUSSION AND CONCLUSION

To evaluate the toxic effect of *Ginkgo biloba* extract (EGb 761) on fertility and general reproductive ability of rats, we examined both F0 and F1 genrations of Sprague-Dawley rats which were exposed to three different concentration ranges of Ginkgo biloba extract (EGb 761) during pregnancy and after delivery.

There was no statistically significant difference of body weight, food and water consumption, copulation rate, the ratio of fertility, and pregnancy in-

Table 18. Pregnancy index of F1 rats

		Control	Low	Middle	High
No. pregnant animal		30	13	33	35
No. corpus Luteum		14.1± 2.9[a]	16.5 ± 4.6	16.8±3.5	15.5± 3.0
No. implantation		11.5± 2.8	12.2 ± 3.4	13.2±2.7	12.1± 2.4
Litter size	\Male	5.6± 2.2	5.7 ± 2.3	6.9±2.0	5.7± 2.2
	\Female	5.6± 1.3	5.9 ± 2.5	6.7±2.1	6.1± 2.3
Dead fetus ratio[b]	\Early	0	0	0	0
	\Late	0	0	0	0
Implantion ratio[c]		81.0±10.6	7.38±12.5	78.3±8.6	78.2±10.2
Resorption ratio[d]		2.2± 4.5	2.6 ± 5.9	1.4±4.1	2.3± 6.1
Sex ratio[e]		1.1± 0.5	1.1 ± 0.6	1.3±0.8	1.3± 1.5

[a]Mean±S.D.
[b](Number of dead fetus/number of implantation)×100.
[c](Number of implantion/number of corpus luteum)×100.
[d](Number of fetus absorbed/number of implantion)×100.
[e]Number of male/number of female.

dex between control and treated rats of F0 generation. No marked extenal, visceral, or skeletal abnormalities were found from fetuses of F0 generation. Based on the results of sex ratio, body weight, fetus number, mental and physical development status, and fertility studies of F1 generation, no significant treatment-related affect was observed throughout the experimental periods.

In conclusion, when Ginkgo biloba extract (EGb 761) was administered up to concentration of 30 mg/kg/day to Sprague-Dawley rats for 2 months, no significant abnormalites of fertility and general reproductive ability in F0 as well as F1 generations was found.

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