

# Protective Effects of Garlic Juice against Embryotoxicity of Methylmercuric Chloride Administered to Pregnant Fischer 344 Rats

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## Abstract

In order to investigate the beneficial effects of 0.5 or 1.0 g/kg Korean garlic juice against the embryotoxicity of 20 mg/kg methylmercury chloride (MMC, CH<sub>3</sub>HgCl), pregnant Fischer 344 rats were simultaneously orally administered on day 7 of gestation. On day 20 of gestation the dams were laparotomized under ether anesthesia, and the fetuses were removed and examined for toxicity of methylmercury. Garlic juice depressed the toxicity in terms of some parameters. In the case of simultaneous treatment with 0.1 g/kg garlic juice and MMC, rates of increase were 17.5% in maternal body weight, 13.2% and 41.9% in fetal and litters' weight respectively, and 37.0% in fetal survival rate. Decreasing rates were 10.0% in maternal death rate, and 6.9% and 31.3% in pre- and post-implantation loss respectively. Decreasing rates of mercury levels in dams were 67.2% in liver, 57.6% in brain, 47.2% in kidney, 42.1% in spleen and 40.9% in blood. As well, decreasing rates of mercury level in fetuses were 54.9% in all body burden, 55.9% in liver, 46.7% in kidney and 37% in brain, respectively. The number of fetal ossification centers were reduced by 23.8% to 58.0% following simultaneous treatment with 1.0 g/kg garlic juice. These findings indicated that garlic juice effectively inhibited the embryotoxicity of methylmercury in pregnant Fischer 344 rats.

**Key Words:** Garlic, methylmercury chloride, protective effect, embryotoxicity

## INTRODUCTION

Methylmercury chloride (MMC) is known to cause serious neurological disorders in adults and infants,<sup>1-4</sup> and it can easily cross the placenta and then accumulate in the fetus, where it can deleteriously affect the offspring.<sup>4,5</sup> Fuyuta et al. and Lee & Han reported that MMC given orally to pregnant ICR mice, C57BL mice, Wistar rats or Fischer 344 rats on day 10 or 7 of gestation caused significant embryotoxic effects.<sup>4,6</sup>

MMC is eliminated mainly in the feces as a result of biliary excretion and exfoliation of intestinal epithelial cells. Intestinal reabsorption occurs due to hepatobiliary recirculation. The enterohepatic recircu-

lation of MMC can be interrupted by the oral application of polythiol resin, which increases fecal excretion.<sup>7</sup> As well, metal chelating agents can be used to aid in the elimination of mercury. Dimercaprol (BAL) and L-cysteine are contraindicated in organic mercury intoxication, because it favors the uptake of mercury into the brain.<sup>7,8</sup> But the more water soluble and less toxic 2,3-dimercapto-1-propan-sulfonate (DMPS) and 2,3-dimercaptosuccinic acid (DMSA), materials which both have thiol group, as well as neutral amino acids such as L-isoleucine, have been shown to create inhibitory effects in methylmercury poisoning.<sup>7-9</sup> The garlic contains many kinds of amino acids. They include some neutral amino acids and numerous thiol groups.<sup>10</sup> Also, they are very potent anti-oxidants against free radicals, which are the results of mercury inhibition in some enzyme systems.<sup>11,12</sup> The purpose of this study was to examine the inhibiting effects of Korean garlic juice against the embryotoxicity of 20 mg/kg MMC by simultaneous treatment with 0.5 or 1.0 g/kg garlic juice to pregnant Fischer 344 rats.

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## MATERIALS AND METHODS

Fischer 344 rats ( $125 \pm 15.7$  g in weight) were obtained from the Experiment Animal Center at Hallym University. They were maintained in clear polypropylene cages and allowed free access to pellet type food (Jeiljedang Co., Seoul) and water during the gestation period. Mature nulliparous females (at the age of 10 wk) in proestrus were caged overnight with mature males about the same age, and the following morning they were examined for signs of a retained intravaginal copulatory plugs. The female was considered mated if sperm were found in a vaginal washing solution or a vaginal plug was detected, and that day was designated day 0 of pregnancy.<sup>13</sup>

The pregnant rats were orally administered 20 mg MMC ( $\text{CH}_3\text{HgCl}$ , Junsei Chemical Co., Tokyo, Japan)/kg body weight with or without Korean garlic juice on day 7 of gestation. The doses of garlic juice were 0.5 or 1.0 g/kg body weight. They were dissolved in saline, and controls were given saline orally. Table 1 shows the content of free amino acids in Korean garlic juice. Each group consisted of 30 females. The dams were laparotomized under ether anesthesia on day 20 of gestation for toxicity examination.<sup>13</sup> The

Table 1. The Content of Free Amino Acids in Korean Garlic Juice

Amino acids		Content (mg/ml)	%
Neutral	Glycine	1.452	2.65
	Alanine	1.669	3.05
	Valine	1.937	3.54
	Leucine	1.859	3.40
	Isoleucine	1.010	1.85
	Serine	1.220	2.23
	Threonine	0.995	1.82
	S-Containing	Cysteine	1.830
	Cystine	9.880	18.05
	Methionine	0.313	0.57
Acidic	Aspartic	4.883	8.92
	Glutamic	7.586	13.85
Basic	Lysine	2.386	4.36
	Arginine	13.398	24.47
Imino acid	Proline	0.972	1.78
Aromatic acid	Phenylalanine	1.719	3.14
	Tyrosine	0.633	1.16
	Histidine	0.996	1.82
Total		54.738	100.0

surviving fetuses were examined for gross toxic effects, sex, size, and weight; half of the fetuses were stained with alizarin red S for skeletal examination,<sup>14</sup> and the others were used for analyzing mercury levels in organs.

Comparisons between the MMC group and the others were performed using the Personal Computer Statistical Analysis System (PC SAS). The confidence limit was  $p < 0.05$ .

## RESULTS

### Maternal weight changes

When the pregnant rats were orally administered 20 mg/kg MMC on day 7 of gestation, their maternal body weights severely decreased, becoming 61.1% of control on day 20 of gestation. However, the maternal weight in groups simultaneously treated with garlic juice were slightly decreased and then recovered quickly. Especially in simultaneous treatment with 20 mg/kg MMC and 1.0 g/kg garlic juice, maternal body weights were 93.6% of control on day 20 of gestation (Fig. 1) (Table 2).

### Resorptions of embryos

The results concerned with the survival of fetuses

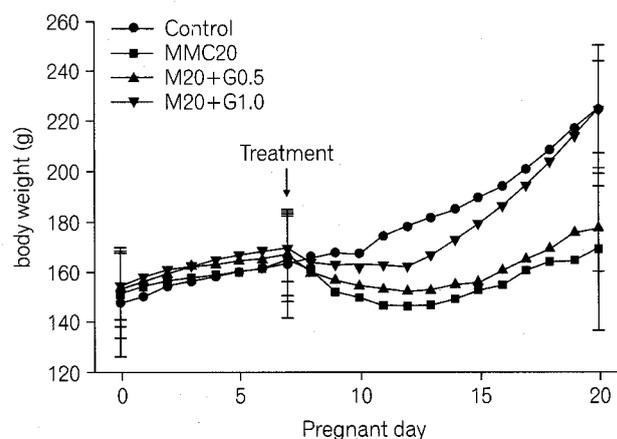


Fig. 1. Increasing rates of maternal body weight in control and treatments; Control, treatment with saline; MMC20, treatment with 20 mg/kg methylmercuric chloride; M20+G0.5 and M20+G1.0, simultaneous treatment with 20 mg/kg methylmercuric chloride and 0.5 or 1.0 g/kg garlic juice.

Table 2. Maternal Body Weight Changes in Control and Treatment Groups during Gestation

Gestation (days)	Control (grams)	MMC20 (grams)	M20+G0.5 (grams)	M20+G1.0 (grams)
0	147.4±20.95	151.5±18.00	153.0±14.67	154.4±13.09
1	150.0±20.96	154.0±17.00	156.2±14.71	158.2±13.47
2	154.2±22.85	156.5±18.44	159.2±13.83	160.6±13.39
3	156.1±22.51	157.5±17.98	162.1±13.05	162.0±13.46
4	158.0±22.15	158.7±17.13	163.4±14.78	164.8±13.82
5	159.7±21.87	160.2±17.47	164.7±16.55	166.3±13.75
6	161.3±21.84	161.2±17.11	165.5±16.72	167.8±13.74
7	163.1±21.26	165.1±18.94	167.3±17.61	169.5±14.67
8	165.5±21.38	160.8±18.85	159.1±13.93	163.5±13.16
9	167.5±21.34	151.9±17.99	156.7±14.75	162.4±14.76
10	167.0±22.08	149.6±17.70	154.6±17.03	163.1±16.18
11	174.2±21.42	146.4±18.72*	153.5±17.46	162.5±16.75
12	178.1±97.32	146.3±19.89*	152.2±18.50*	161.8±16.71
13	181.4±21.98	146.0±20.17*	152.8±18.29*	166.7±16.85
14	184.4±19.76	148.9±20.44*	154.8±21.69	172.9±16.96
15	189.6±21.29	152.5±22.92*	155.8±22.74	179.1±19.88
16	193.9±18.38	154.4±25.68*	160.3±21.37	186.5±16.11
17	200.6±20.46	160.5±27.72	164.8±20.48	194.3±15.64
18	208.3±22.36	163.3±29.72	168.8±18.04	203.7±16.35
19	216.9±23.77	164.5±33.12	175.4±19.34	214.1±16.50
20	224.6±25.44	169.0±32.18	177.3±17.13	225.4±17.90

Values are given as mean±standard deviation; each group consisted of 30 females; MMC20, 20 mg/kg methylmercuric chloride; M20+G0.5 and M20+G1.0, 20 mg/kg methylmercuric chloride and 0.5 or 1.0 g garlic juice.

\* significantly different from control at  $p < 0.05$ .

are summarized in Table 3. Maternal death rate was 13.3% in the 20 mg/kg MMC group, but in simultaneous treatment with 0.5 or 1.0 g/kg garlic juice, the rates decreased to 10.0% and 3.3%, respectively. The fetal survival rate was 48.7% in the 20 mg/kg MMC group, but in the group simultaneously treated with garlic juices, the rates increased 55.8% and 85.7% respectively compared to the control group. Pre- and post-implantation losses were 22.3% and 39.4% in 20 mg/kg MMC group (11.4% and 2.0% in the control group), but significantly decreased to 15.4% and 8.1% respectively in the group simultaneously treated with 1.0 g/kg garlic juice.

#### Mean weights of fetuses and litters

The mean weight of fetuses in 20 mg/kg MMC group was 76.5% of control (mean±S.D., 3.70±0.23 g). However, as shown in Table 3 in the group simultaneously treated with 0.5 and 1.0 g/kg garlic juice, fetal weight increased by 79.7% and 89.7% respectively compared to the control group. The mean weight of litters in the 20 mg/kg MMC group

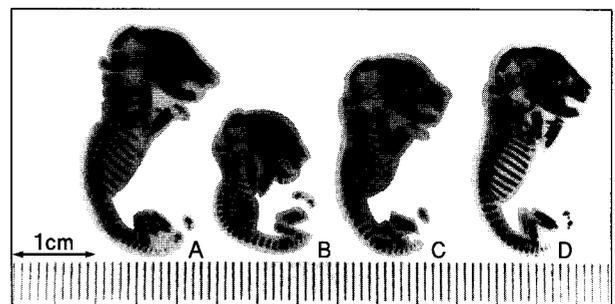


Fig. 2. Fetal skeletons in rats orally administered methylmercuric chloride with/without garlic juice on day 7 of gestation, photographs stained with alizarin red S. (A) Fetal skeleton of control group. (B) Fetal skeletons in rats orally administered 20 mg/kg methylmercuric chloride. (C, D) Fetal skeletons in rats simultaneously orally administered 20 mg/kg methylmercuric chloride and 0.5 or 1.0 g/kg garlic juice, respectively. Note decreased size, delayed ossification and lordosis with exposure of methylmercuric chloride. However, they recovered to become similar to controls according to the increase in the dose of garlic juice.

was 33.6% of control (mean±S.D., 39.6±0.67 g). But in the group simultaneously treated with 0.5 and 1.0 g/kg garlic juice, they were significantly increased by 47.5% and 75.5% of control group, respectively.

Table 3. Effects of Garlic Juice Treated with Methylmercuric Chloride Given Orally on Day 7 of Gestation in Pregnant Fisher 344 Rats

Parameters	Control	MMC20	M20+G0.5	M20+G1.0
Number of dams	30	30	30	30
Maternal death (%)	0 (0.0)	4 (13.3)	3 (10.0)	1 (3.3)
Total live fetuses	308	150	172	264
Live fetuses (number per litter, mean $\pm$ S.D.)				
Male	5.2 $\pm$ 2.81	3.0 $\pm$ 1.29*	3.3 $\pm$ 2.10	4.7 $\pm$ 1.06
Female	5.1 $\pm$ 2.07	2.7 $\pm$ 1.28*	3.1 $\pm$ 1.91*	4.4 $\pm$ 1.41
Total	10.3 $\pm$ 1.83	5.7 $\pm$ 1.59*	6.4 $\pm$ 2.09*	9.1 $\pm$ 1.60
Live fetus (body weight, grams, mean $\pm$ S.D.)				
Male	3.78 $\pm$ 0.25	2.88 $\pm$ 0.45*	2.98 $\pm$ 0.26	3.39 $\pm$ 0.34
Female	3.62 $\pm$ 0.18	2.78 $\pm$ 0.45*	2.93 $\pm$ 0.30	3.25 $\pm$ 0.27
Average	3.70 $\pm$ 0.23	2.83 $\pm$ 0.45*	2.95 $\pm$ 0.28	3.32 $\pm$ 0.24
Live litter (body weight, grams, mean $\pm$ S.D.)				
Male	20.1 $\pm$ 1.03	7.2 $\pm$ 0.74*	9.8 $\pm$ 0.74	14.6 $\pm$ 0.21
Female	19.5 $\pm$ 0.77	6.1 $\pm$ 0.61*	9.1 $\pm$ 0.61*	15.3 $\pm$ 0.27
Total	39.6 $\pm$ 0.67	13.3 $\pm$ 1.02*	18.8 $\pm$ 1.02*	29.9 $\pm$ 0.44
Live fetus (body length, mm, mean $\pm$ S.D.)				
Male	32.9 $\pm$ 1.40	25.6 $\pm$ 1.02*	27.9 $\pm$ 1.35*	31.9 $\pm$ 1.72
Female	31.1 $\pm$ 1.23	24.8 $\pm$ 1.28*	26.6 $\pm$ 1.06*	30.0 $\pm$ 1.86
Average	32.0 $\pm$ 1.56	25.2 $\pm$ 1.19*	27.2 $\pm$ 1.36*	31.0 $\pm$ 2.01
Corpora lutea (mean $\pm$ S.D.)	11.5 $\pm$ 2.61	12.1 $\pm$ 1.79	11.8 $\pm$ 2.05	11.7 $\pm$ 1.68
Implantation sites (mean $\pm$ S.D.)	10.3 $\pm$ 1.83	9.4 $\pm$ 1.45	9.6 $\pm$ 1.99	9.9 $\pm$ 1.64
A (%)	11.4 $\pm$ 1.58	22.3 $\pm$ 1.52*	18.6 $\pm$ 2.72*	15.4 $\pm$ 2.04
B (%)	2.0 $\pm$ 1.86	39.4 $\pm$ 3.42*	33.3 $\pm$ 3.75*	8.1 $\pm$ 1.86
C (%)	13.4 $\pm$ 2.12	52.8 $\pm$ 2.02*	45.8 $\pm$ 3.35*	22.2 $\pm$ 2.04

MMC20, 20 mg/kg methylmercuric chloride; M20+G0.5 and M20+G1.0: 20 mg/kg methylmercuric chloride and 0.5 or 1.0 g garlic juice; A, pre-implantation loss (%) = (number of corpora lutea - number of implantation)/number of corpora lutea \* 100; B, post-implantation loss (%) = (number of implantation - number of live fetuses)/number of implantation \* 100; C, total-implantation loss (%) = (number of corpora lutea - number of live fetuses)/number of corpora lutea \* 100.

\* significantly different from control at  $p < 0.05$ .

### Mean fetal body lengths

The fetal body lengths were affected by methylmercury, and their mean length was 78.8% of the control group. As shown in Fig. 2, the backbones of fetuses were severely curved resulting from the mercury dose. However, in the group simultaneously treated with 0.5 and 1.0 g/kg garlic juice, fetal body lengths significantly increased by 85% and 96.9% respectively compared to the control group.

### Mercury levels

Table 4 shows the mercury levels (mg/wet kg) in maternal and fetal organs for each group.

### Fetal ossification centers

The numbers of fetal ossification centers stained with alizarin red S (Table 5) were counted. Fetal ossification centers in the 20 mg/kg MMC group were not completely formed at pectoral and pelvic phalanges, sternbrae and tail, and they developed to be 53.5%, 35.1%, 74.1% and 76.2% of the control

Table 4. Mercury Concentration in Maternal and Fetal Organs of Fischer 344 Rats Orally Administered Methylmercuric Chloride with/without Garlic Juice on Day 7 of Gestation

Organs	Control (mg/wet kg)	MMC20 (mg/wet kg)	M20+G0.5 (mg/wet kg)	M20+G1.0 (mg/wet kg)
<b>Adults</b>				
Kidney	0.08±0.010	94.05±9.848	88.21±6.763	49.70±7.335
Spleen	0.29±0.029	44.21±4.007	40.60±3.497	25.58±2.886
Blood	0.04±0.016	39.22±2.320	39.43±2.820	23.16±2.771
Liver	0.01±0.005	18.74±1.680	12.16±2.475	6.14±1.332
Brain	0.03±0.015	5.68±0.737	3.52±0.246	2.41±0.482
Placenta	0.01±0.004	8.96±0.676	6.95±0.246	4.81±0.660
<b>Fetuses</b>				
All body	0.02±0.005	8.80±0.513	5.75±0.262	3.97±0.652
Liver	0.19±0.027	31.24±2.191	21.80±1.127	13.79±1.167
Kidney	1.47±0.231	13.86±0.773	11.44±0.838	7.39±1.073
Brain	0.29±0.053	11.24±0.316	9.54±0.471	7.08±0.478

MMC20, 20 mg/kg methylmercuric chloride; M20+G0.5 and M20+G1.0, 20 mg/kg methylmercuric chloride and 0.5 or 1.0 g garlic juice.

Table 5. Number of Fetal Ossification Centers in Fischer 344 Rats Orally Administered Methylmercuric Chloride with/without Garlic Juice on Day 7 of Gestation

Bone	Control	MMC20	M20+G0.5	M20+G1.0
Pectoral phalanges	15.9±0.32	8.5±1.84*	10.7±0.82*	14.8±1.40
Pelvic phalanges	11.4±0.70	4.0±2.62*	8.6±1.58*	10.9±0.99
Sternebrae	5.8±0.42	4.3±0.82*	4.6±0.70*	5.4±0.52
Tail	10.1±0.32	7.7±0.48*	8.0±0.67*	10.2±0.63

MMC20, 20 mg/kg methylmercuric chloride; M20+G0.5 and M20+G1.0, 20 mg/kg methylmercuric chloride and 0.5 or 1.0 g garlic juice.

\* significantly different from control at  $p < 0.05$ .

group, respectively. However, in the group simultaneously treated with 0.5% and 1.0 g/kg garlic juice, they significantly increased to be 67.3% and 93.1% at pectoral phalanges, 75.4% and 95.1% at pelvic phalanges, 79.3% and 93.1% at sternebrae, and 79.2% and 100% at tail respectively, compared to the control group.

## DISCUSSION

The results of this study demonstrate the inhibitory effects of Korean garlic juice against the embryotoxicity of 20 mg/kg MMC when these compounds were simultaneously treated to Fischer 344 rats on day 7 of gestation. The maternal, fetal and litter's weight,

the number of corpora lutea, total implantations and resorptions, the mortality of dams and fetuses, the mercury level in organs, as well as the number of fetal ossification centers were significantly different than the MMC group, but were no different from the control group. They were particularly significant in the treatment group of 1.0 g/kg garlic juice. These findings indicate that a high dose of garlic juice could decrease the embryotoxicity of MMC in rats. They also suggest, by implication, that human beings may be similarly affected.

Significant decreases in maternal, fetal and litter weights have been previously reported when MMC was orally administered to pregnant rats at different dose-levels and at different stages of gestation.<sup>4,6,12</sup> There are complex and multi-factorial conditions in

maternal weight changes. One of the major causes was reported to be anorexia, which precedes the clinical signs of nervous system injury in experimental animals, and fetal effects.<sup>15,16</sup> However, the maternal weights recovered quickly following garlic treatment, which may play the role of flavor<sup>17</sup> and nutrient.<sup>10</sup> Other causes were related to fetal and litter weights. Methylmercury, when present during developmentally-sensitive periods, particularly during the days of rapid organogenesis, produces increased fetal mortality and malformations even at relatively low levels.<sup>6</sup> Malformed fetuses may be lighter because of some inherent sensitivity to exposure in the embryo that slows development and becomes manifest as both adverse effects. As well, fetuses that develop a malformation early in gestation may be less able to use nutrients, and hence are more susceptible to being of low birth weight. However, our's and some other studies have revealed that garlic may help to boost the birth-weight of babies otherwise destined to be too small, such as adding garlic extracts to the placenta cells of women likely to suffer from these conditions to quickly stimulate growth.<sup>18</sup> Furthermore, they reported that the activity of key enzymes which are reduced in abnormal pregnancies were significantly increased when garlic was added. The drastic change of maternal weight by methylmercury treatment is probably due to the high incidence of fetal resorptions, the high pre- and post-implantation loss,<sup>4,12,13</sup> and the lower mitotic growth rate in the affected fetuses.<sup>6,12,19</sup> These effects of garlic may have made implantation loss significantly different from the MMC group, but similar to the control group in our study.

Methylmercury administered orally was significantly retained in liver, kidney, spleen and brain.<sup>1,4,20,21</sup> The results of our study showed that mercury levels were significantly reduced by simultaneous treatment with garlic juice in maternal and fetal organs. Exposed methylmercury is eliminated mainly in the feces as a result of biliary excretion and exfoliation of intestinal epithelial cells. Intestinal reabsorption occurs due to hepatobiliary recirculation. The enterohepatic recirculation of methylmercury can be interrupted by the oral application of polythiol resin-like garlic, which increases fecal excretion.<sup>7</sup> As well, metal-chelating agents can be used to aid in the elimination of mercury. Dimercaprol (BAL) and L-cysteine are contraindicated in organic mercury intoxication be-

cause it favors the uptake of mercury into the brain.<sup>7,8</sup> Although garlic juice contains L-cysteine, it reduced mercury levels in the brain as well as other organs in our study. Garlic contains numerous neutral amino acids, such as L-phenylalanine and L-isoleucine, which can suppress the brain uptake of methylmercury.<sup>7,8,22</sup> Methylmercury easily passes through the placenta<sup>5</sup> and accumulates in fetal tissue at concentrations that sometimes exceed those in the mother.<sup>4,23</sup> However, our study showed that garlic suppressed mercury from crossing the placenta, and then significantly reduced mercury levels in fetal liver, kidney and brain, although they were a little higher than those in the maternal organs. As well, garlic juice increased the delayed ossification of fetuses caused by the absence of one or more sternbrae and incomplete ossification of the bilobed vertebral center by treatment with methylmercury.<sup>4,6,12</sup>

Mercury has long been known as a binder of proteins forming strong mercaptide bonds with sulfhydryl groups and other anionic protein chains resulting in denaturation and deactivation of protein molecules.<sup>19,24-26</sup> These poisoned enzyme systems caused the inhibition of protein synthesis, resulting in a decreased rate of cell growth and development by reduced energy supply in a subcellular mechanism of enzymes.<sup>12,27-29</sup> The inhibitory effects of garlic juice against the toxicity of methylmercury may be related to the protection of these enzyme systems. Since garlic contains some amino acids which have many thiol groups, methylmercury may chelate with them instead of enzymes. Also, as a very potent antioxidant, garlic may provide protection against increasing free radical formation by the inhibition of enzyme systems causing methylmercury, resulting in increased DNA damage.<sup>11,12,18</sup>

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