# The Effects of *Panax ginseng* on TCDD-induced Testicular Atrophy in Guinea Pigs

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ABSTRACT

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), one of the most notorious toxic environmental pollutants, induces various toxic effects in many organs including testes and is regarded as an endocrine disruptor. Korean ginseng, on the other hand, has been well-known for its preventive effects on toxins, diabetes melltus and hyperlipidemia. We investigated, histopathologically, the effect of Korean Red ginseng water extract (KR-WE) on guinea pig testes damaged by TCDD. Ninety guinea pigs were divided into 6 groups : normal control (NC) group received vehicle and saline; TCDD, 1$\mu$g/kg b.w., was administered intraperitoneally to the single dose TCDD-treated (TT) group; 100 mg/kg b.w./d and 200mg/kg b.w./d KR-WE were injected intraperitoneally to the preventive groups (P100 and P200, respectively) for 28 days from 1 week before TCDD injection; and to the therapeutic groups (C100 and C200, respectively) for 14 days since 1 week after TCDD administration. Increment of body weight was retarded to a larger extent by TCDD. Moreover, body weight of the TT group decreased significantly 7 days after TCDD exposure, while that of preventive groups kept increasing. Decrease in body weight was not observed in KR-WE-treated groups. Weight decrease in testes caused by TCDD was remarkably protected by KR-WE. Testicles in TT group displayed decreased tubular size and maturation arrest at the primary or secondary spermatocyte stage. On the other hand, maturation arrest in germ cells by TCDD was improved in KR-WE treated groups. Almost complete protection of the testes was observed in P100 and P200 groups. In addition, the therapeutic effect was noticed in C100 and C200 groups. These results provided strong evidence that Korean Red ginseng might be a useful agent for the prevention and treatment of testicular damage induced by environmental pollutants.

## Introduction

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), which belongs to the group of polyhalogenated aromatic hydrocarbons, has been known to be the most potent toxic environmental pollutant. The more

serious problem is that TCDD is still being generated by municipal garbage incinerators, exhaust from leaded gasolins and pulp industries. Most recently, it received a great deal of worldwide attentions as an endocrine disruptor. In animal studies, exposure to TCDD either in adulthood or during late fetal and early postnatal development causes a variety of adverse effects on the male reproductive system[1-3]. Decreases in spermatogenesis, and the ability to conceive and carry a pregnancy to term are the most sensitive signs of reproductive toxicity by TCDD in mammals[4]. On the other hand, Korean Red ginseng (*Panax ginseng* C.A. Meyer) has been used from ancient times for the prevention and treatment of a variety of pathologic conditions, associated particularly with aging. Recently, it has been found that ginseng protected the body from diabetes mellitus[5], hyperlipidemia[6], immune dysfunction[7], and toxic substances[8] by a number of different enhancing and/or inhibitory mechanisms.

In spite of the severe testicular damage of TCDD, there has been no studies on the prevention or therapy against the toxicity of TCDD. Therefore, attempts have been made to investigate the beneficial role of Korean Red ginseng on the TCDD-induced testicular damage. In this histopathologic observation we found that Korean Red ginseng had protective and therapeutic effects on testicular atrophy and arrest of germ cell maturation induced by TCDD.

## Materials and Methods

*Experimental animals*

Four- to 5-week-old male guinea pigs (180-200 mg, Hartley) were purchased from Samyuk Hi-Quality Laboratory Animal Inc., Osan City, Kyunggi Province, Korea. They were provided with solid rabbit food (Purina Co., Ltd.) and water *ad libitum*, and kept at constant temperature (24±1℃) and humidity (60±10%) on a 12 hr light/12 hr dark cycle. They were employed for the experiment at least 5 days after delivery from the breeding company. Fresh cabbage, instead of vitamin C, was supplemented twice a day.

*Chemicals*

TCDD was purchased from Cambridge Isotope Laboratories Inc., with >99.9% purity as judged by gas chromatography. It was dissolved in acetone by sonication, diluted with corn oil and vortexed vigorously just before use. Corn oil was procured from a local retail store. All other biochemicals were purchased from Sigma, St. Louis, MO, and were of the highest purity available.

*Preparation of Korean Red ginseng water extract (KR-WE)*

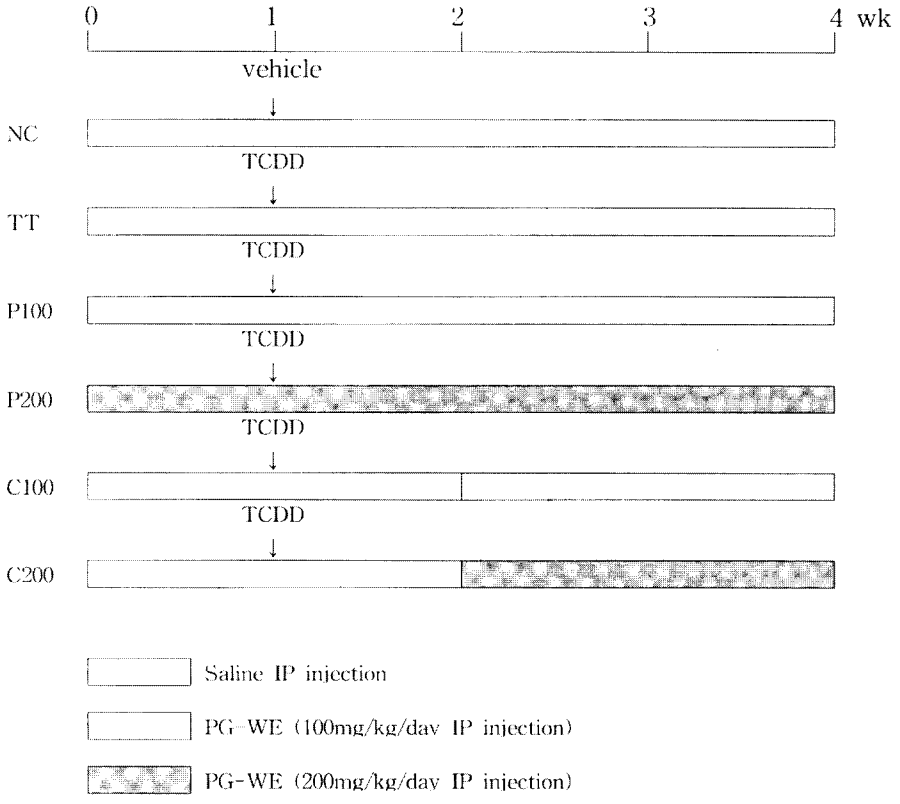
Six-year-old fresh *Panax ginseng* root was kindly supplied by the Jungpyong Experimental

Station, Korea Ginseng and Tobacco Research Institute, Chungbuk, Korea. It was washed with tap water, steamed at 98℃ for 3 hrs and dried at 72℃ for 48 hrs to produce Korean Red ginseng. The dried red ginseng was then extracted with 10 volumes of water at 80℃ for 8 hrs three times, filtered and concentrated the pooled filtrate under the reduced pressure to obtain a darkish brown syrup. Process of red ginseng and its water extract was carried at the Korea Ginseng plant at Puyo, Chungnam Province, Korea.

*Administration of TCDD and KR-WE*

Ninety guinea pigs were divided into 6 groups (Fig. 1): normal control (NC) group received vehicle (corn oil and trace amount of acetone) and saline; TCDD, 1$\mu$g/kg b.w., was administered intraperitoneally to the single TCDD-treated (TT) group; 100 mg/kg b.w./d and 200 mg/kg b.w./d KR-WE were injected intraperitoneally to the preventive groups (P100 and P200, respectively) for 28 days from 1 week before TCDD injection; and to the therapeutic groups (C100 and C200, respectively) for 14 days since 1 week after TCDD administration.

Fig. 1. Experimental protocol for the effect of PG-WE on TCDD-treated male guinea pigs



*Blood sampling and isolation of testicle*

Solid food and water were removed 1 day before sacrifice. Blood sampling was made directly from heart puncture and the testicle was removed under general anesthesia with ethyl ether. The testicle was weighed, and fixed by submerging it into the Bouin solution and 2.5% glutaraldehyde for histopathological study.

*Light microscopic evaluation*

In order to investigate histologic changes, Bouin-fixed and paraffin embedded testicular tissues were sliced to 4-6 $\mu$m in thickness, stained with H&E (haematoxylin and eosin) and observed under a light microscope. Approximately 50 horizontally cut seminiferous tubules in each group were calculated for measuring tubular size. All seminiferous tubules in one histologic section of testicular specimen were evaluated and scored from 1 to 10 using Johnsen's scoring system (Table 1).

**Table 1**. Testicular biopsy score counts

| Score | Description of scoring system |
|---|---|
| 10 | Complete spermatogenesis with many spermatozoa (determined by head form)<br>Germinal epithelium organized in regular thickness leaving an open lumen |
| 9 | Many spermatozoa present but germinal epithelium disorganized with marked sloughing or obliteration of lumen |
| 8 | Only a few spermatozoa present (<5 to 10) |
| 7 | No spermatozoa but many spermatids present |
| 6 | No spermatozoa and only a few spermatids present (<5 to 10) |
| 5 | No spermatozoa and no spermatids but several or many spermatocytes present |
| 4 | Only a few spermatocytes (<5) but no spermatids or spermatozoa present |
| 3 | Spermatogonia are the only germ cells present |
| 2 | No germ cells, but Sertoli cells are present |
| 1 | No cells in tubular section |

Data from Johnsen SC: Hormones 1:2, 1970.

*Statistical analysis*

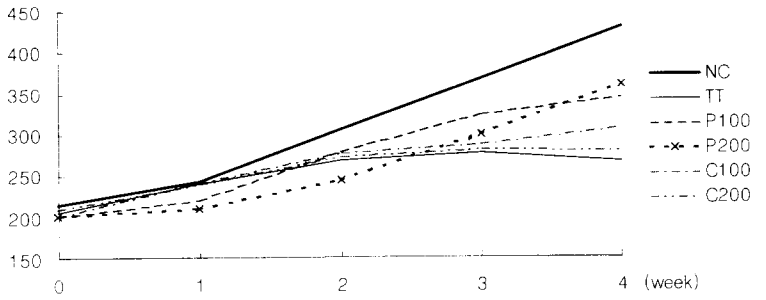
Data was obtained for 15 animals from each group and was presented as mean values and standard deviations. Data for body weights was statistically analyzed using variance analyses followed by Dunnett's test, those for testicular weights and tubular sizes were analyzed with Student's *t* test. The level of significance chosen in all cases was $P<0.05$.

## Results

*Body weight*

As shown in Fig. 2, there was a significant decrease in body weight gain from 7 days after TCDD-treatment in TCDD exposed groups. In addition, decrease in body weight was observed in TT group from 14 days after TCDD-exposure. Although the increment of body weight in P100 and P200 groups was lower than that in NC group, the loss in body weight was not observed. Increase in body weight of P200 group was much slower than that of the other groups for the first 3 weeks but there was not a great difference in body weight at the 28th day between P200 and NC groups. The rate of weight gain in C100 and C200 groups was greatly slowed by TCDD treatment. Although weight loss was not observed in C100 and C200 groups, there was not significant difference in the rate of weight gain between C and TT groups.

Fig. 2. Changes in body weight of guinea pigs in each group




*Testicular weight*

Testicular weight in TT group was reduced significantly compared with NC group. This difference in testicular weight was unlikely to be accredited to a selective loss of testicular tissue as a result of TCDD treatment. No differences were noticed when testicular weight was expressed as a percentage to body weight. Testicular weights in P and C groups were not attenuated compared with TT and NC groups, thus demonstrating that ginseng had both protective and therapeutic effects on the TCDD-induced testicular atrophy (Table 2).

*Light microscopic findings*

Tubular cross section of normal testes showed well-arranged occupation of cells in all different stages (Fig. 3). Spermatogonia and Sertoli cells rested on the basement membrane and were sur-

**Table 2**. Body and testicular weights of guinea pigs in each group

| Group | BW(gm) | TW(gm) | TW/BW(%) |
|---|---|---|---|
| NC | 429.9±23.0 | 3.0±0.2 | 0.7 |
| TT | 267.5±11.8 | 1.9±0.5 | 0.71 |
| P100 | 345.5±30.3 | 2.7±0.5 | 0.78*,** |
| P200 | 360.4±24.3 | 3.3±0.3 | 0.92*,** |
| C100 | 307.1±2.3 | 2.4±0.1 | 0.78*,** |
| C200 | 281.1±2.3 | 2.4±0.1 | 0.85*,** |

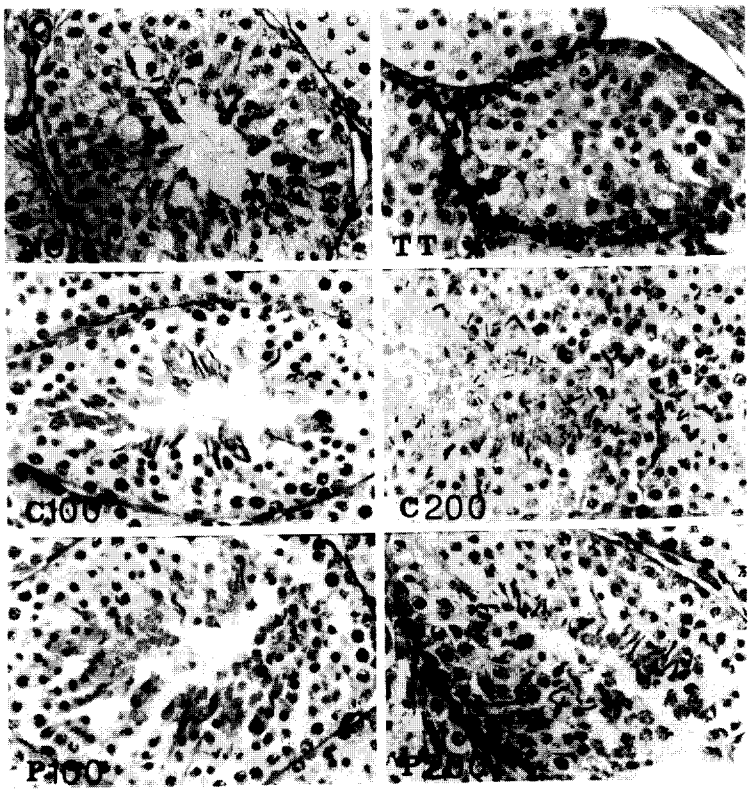
BW : body weight, TW : testicular weight

a : Data were analyzed with unpaired Student's *t* test

* : Significantly different from NC group, $p<0.05$

**: Significantly different from TT group, $p<0.05$

Fig. 3. Light micrograph of testicular tubules (H&E, x 40)



rounded by a concentric myofibroblast layer similar to human testis. Leydig cells were scattered within the interstitium. However, maturation of spermatogonia in TT group was halted at the primary or secondary spermatocyte stage. Mainly late phase spermatids, being radially arranged with a narrow oval head and pale chromatin were observed. Seminiferous tubular size decreased compared with normal testis (Table 3). Only a few spermatozoa were seen in occasional tubules and no pyknotic bodies were present.

**Table 3**. Seminiferous tubular size in each group

| Group | Tubular size(㎛) |
|---|---|
| NCa | 214±19 |
| TT* | 150±31 |
| P100 | 210±18 |
| P200 | 210±13 |
| C100 | 205±18 |
| C200 | 206±15 |

a: Data were analyzed with independent-samples Student's *t* test.

* : Significantly different from NC group, $p<0.05$

In C100 group, the majority of sperm cells were mature spermatids, being peripherally placed with less dense chromatin. Less than 10 spermatozoa were seen and no pyknotic bodies were observed in C100 testes. In C200 group, fully matured spermatozoa with dense nuclear chromatin were frequently noted. A few immature spermatozoa were also observed in the seminiferous tubules of C200 testes. In P100 and P200 groups, as in normal control, fully mature hooked spermatozoa with dense nuclear chromatin were observed in almost all tubules, including the presence of pyknotic bodies. Sertoli cells were well preserved in P group testes.

There was no difference between NC and P200 groups in mean score counts as shown in Table 4. Sixty seven percent of the tubules scored 10 in P100 group. On the other hand, 80% of tubules in TT group scored 6 and the main pathologic feature was the late maturation arrest. Score counts for C200

**Table 4**. Mean score counts with Johnson' s scoring system in each group

| Group | Mean score |
|---|---|
| NC | 10.0 |
| TT | 6.7 |
| P100 | 9.7 |
| P200 | 10.0 |
| C100 | 7.6 |
| C200 | 8.5 |

group were 10 in 40%, 9 in 13% and 7 in 47%. Meanwhile 67% of the tubules scored 7 in C100 group.

## Discussion

TCDD, the most thoroughly studied compound as it is the most potent toxic environmental pollutant, serves as the prototype of the halogenated aromatic hydrocarbons. TCDD is formed as a contaminant in the organic synthesis of 2,4,5-trichlorophenol, being used to manufacture 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), a broad spectrum herbicide and defoliant[9]. Although toxicity and dominant lethal studies with TCDD have been reported by many researchers, it is difficult to appreciate its severity from the literature because the toxic effects observed vary depending on dose, length of exposure (acute *vs* chronic), and most remarkably, the species of animal. Animal species vary greatly in their sensitivity to TCDD. The acute oral $LD_{50}$ of TCDD varies over a 5000-fold range in different species [$LD_{50}$ ($\mu$g/kg)] : guinea pig, 1[10]; rat (male), 22, (female), 45[10]; monkey, <70[11]; rabbit, 115[10]; mouse, 114[12,13]; dog, >300[10]; bull frog, >500[14]; hamster, 5000[15,16]. This large variation in species sensitivity to TCDD is not accounted by an appreciable difference in the rate of metabolism of TCDD. Therefore, the toxic effects of TCDD on fertility in male mammals have been diverse. TCDD-treated expermental animals displayed decreased spermatogenesis[4,17] or no change of spermatogenesis[18], reduced ejaculated sperm numbers[19] and reduced fertility as a consequence of the direct action of TCDD on the epididymis, including delayed puberty and altered reproductive organ weights[20]. Histological examination of testes showed normal, but the epididymides were inflamed with sperm granuloma formation which was analogous to changes seen in the autoimmune reaction following bacterial infection or the response of tissues to foreign bodies[21]. Other evidence that the TCDD produced adverse effects in the testes was reported by Van Miller and Allen[22]. In their study, male Sprague-Dawley rats were fed diets containing various levels of TCDD for 65 weeks. Animals receiving 0.05, 0.5 and 1.0 ppm of TCDD in their food diet within 4 weeks, and the autopsy showed a noticeable decrease in spermatogenesis. Seiler[23] reported that 0.4 mg/kg b.w. dose of TCDD administered intraperitoneally to male mice produced an approximate 50% reduction in the rate of testicular DNA synthesis. TCDD and its congeners have also been implicated in causing adverse effects in the testis of a number of other animals[24,25]. The fact is clear in that TCDD apparently reaches the testes[22-26]. Even though reduced testicular weight after TCDD treatment was observed, this decrease was unlikely to be due to a selective loss of testicular tissue as shown in Table 2. Testicles in TT group displayed decreased tubular size and the maturation arrest at primary or secondary spermatocyte stage. Tubular size in TT group decreased compared to normal control, which could have resulted from a general size reduction of the testis, rather than selective loss of testicular tissue. These findings were consistent with Van Miller and Allen' s report[22].

Advances in biochemical and hormonal research in the area of male reproduction, and improved methods of artificial insemination might be combined with medical therapy to enhance a couple's fertility outcome. However, results are variable depending on the etiology of male infertility. Generally, it is preferable to try to improve spermatogenesis rather than to ignore the male factor. In a clinical setting, many empirical treatments have been applied to patients for improving quality and number of sperm. But the results still have not been promising[27,32].

Ginseng is used to replenish vital energy and to promote the secretion of body fluids for treatment of shock and prostration. It has also been shown that ginseng possessed the effects of stimulating the central nervous system, cardiotonic function, antifatigue action, mechanism of hematopoiesis, and enhancing the immune system. Extensive research has shown that ginseng contains medicinally useful substances such as ginsenosides, minerals-iron, copper, zinc, Mn, Mg, germanium, phosphorus, sulfur, *etc.,* enzymes, carbohydrates, amino acids, peptides, proteins, flavonoids, essential oils, fatty acids, phytosterols, crude fibers, adenosine, maltol, and phenolic compounds[33].

Increment of body weight was retarded to a larger extent by TCDD, while body weight in P groups increased at a similar rate to normal control. This finding confirmed the preventive effect of ginseng on wasting syndrome induced by TCDD. Slow increase in body weight of P200 group during the first 3 weeks might be due to pain stress induced by a larger intraperitoneal injection of PG-WE. But there was little difference in body weight changes between C and TT groups. It may not be from a lack of therapeutic effect but be due to the short-term treatment of KRG-WE. However, we could not extend the experimental period longer than 4 weeks because most of the TT group animals showed severe weakness.

Ginseng revealed both protective and therapeutic effects on TCDD-induced testicular atrophy. Maturation arrest in germ cells by TCDD was remarkably protected in KRG-WE-treated groups. Especially, nearly complete protection of the testes was observed in pretreated groups. In addition, therapeutic effect of KRG-WE was also noticed in post-treated groups, thus indicating therapeutic effects of KRG-WE. More favorable therapeutic effects of ginseng against wasting and testicular damage could be expected if duration of ginseng treatment in C groups were extended.

These results provided evidence that ginseng might be a useful agent for the prevention and therapy of testicular damage induced by environmental pollutants. Further investigation with oligospermic male patients is required to assess the clinical effects and the mechanism of treating infertility by ginseng or by its active components.

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