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# Evaluation of Radiomodifying Effects of Root Extract of *Panax ginseng*

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**Radiomodifying effects of the root extract of *Panax ginseng* were observed on the testes of Swiss albino mice at 10 and 20 mg/kg dose. The root extract was found to be non-toxic when injected up to 1200 mg/kg. A significant enhancement was observed in the survival time of the irradiated group compared with the control when pretreated with ginseng extract. Besides survival time, radiation induced damage to the germ cells and loss of body weight were also reduced markedly by this treatment. The probable reason for this radioprotection can be correlated with the increased level of liver glutathione (GSH). © 1997 John Wiley & Sons, Ltd.**

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*Keywords:* radioprotection; testis; glutathione; ginseng

## INTRODUCTION

Since the discovery of sulphhydryl compounds (Dale, 1942), several radioprotective compounds have been discovered and synthesized. However, their toxicity limits their clinical use. In the search for less toxic radioprotectors various plant extracts have been evaluated in laboratory animals. Ginseng is one of those plant products which has been shown to be effective on radiation caused bone marrow deaths (Takeda *et al*., 1982).

Ginseng, a native plant of Korea and China exhibits various pharmacological and clinical applications (Heu, 1983; Ambasta, 1992). Its crude extracts and thermally stable fractions were evaluated for its radioprotective potency (Yonezawa, 1976). Various studies have been done to compare the efficacy of different fractionated components of ginseng and of the crude extract. It has been reported that the crude extract is more effective in terms of radiation response than any of its fractions individually (Zhang and Chen, 1987). Therefore more systematic studies are needed to assess the radioprotective effects and mode of action of the crude extract of ginseng.

In the present study, an attempt has been made to evaluate the modification of radioresponse in the testes of Swiss albino mice in the presence or absence of ginseng. The rationale for observing the effects on the testes is its highly proliferative and differentiating cells which are radiosensitive. The protection of these cells is of prime importance since any harmful effect of radiation exposure may pass through generation to generation.

## MATERIALS AND METHODS

**Animals.** Swiss albino mice (6–8 weeks old) were used for the present study. Animals were given standard mouse food and water *ad libitum*. The colony was maintained at a room temperature of 25°±2 °C and a light:dark exposure of 12:12 h.

**Source of irradiation.** Animals were irradiated by a $Co^{60}$ source in the cobalt therapy unit at SMS Medical College, Jaipur, India. For irradiation the animals were kept in a ventilated plastic box at a distance of 80 cm from the source. The dose rate of the source at this distance was 1.69 Gy/min.

**Chemical.** Root extract of *Panax ginseng* was obtained from Amsar Pvt. Ltd., Indore, India in dry powdered form. It was dissolved in distilled water before injection.

**Design of experiment.** Animals were given ginseng extract treatment continuously for 4 days via intraperitoneal (i.p.) injection in 0.1 mL of distilled water. On the last day (i.e. day 4) they were irradiated 30 min after injection and this day was considered as day 0. Animals were then autopsied on days 1, 3, 7, 14 and 30. Their testes were taken out and processed for histopathological observations. Other parameters studied were animal body weight, testes weight and mortality.

To evaluate radiation effects and radioprotective efficacy and toxicity of ginseng extract animals were divided in different groups as follows.

**Group I.** To study normal animals, only 0.1 mL distilled water as vehicle was injected.
**Group II.** To evaluate acute toxicity of ginseng extract it was injected at 10, 20, 60, 600, 800 and 1200 mg/kg body weight dose level to different groups of animals.
**Group III.** To study toxic effects of ginseng in 30 days, two dose levels, i.e. 10 and 20 mg/kg were given to two groups of animals.
**Group IV.** As a radiation treated control, animals were exposed to $LD_{50/30}$ dose of radiation, i.e. 8 Gy on day 0 without any other treatment.
**Group V.** To study the radioprotective efficacy of ginseng, it was injected at 10 and 20 mg/kg dose levels and on day 0 animals were irradiated with 8 Gy $\gamma$-radiation.
**Group VI.** To estimate liver glutathione (GSH) level animals were divided into five subgroups, as normal, irradiated control and ginseng treated (at 10, 20 and 60 mg/

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kg dose levels) subgroups. In this series animals were treated continuously for 10 days before irradiation.

**Estimation of GSH.** Liver glutathione and acid soluble sulphhydryl (–SH) groups were measured by the method of Moron *et al*. (1979). However, it is briefly described as follows. A homogenate of liver was prepared in KCl buffer which was immediately precipitated with an equal volume of 25% TCA (trichloro acetic acid) and the precipitate was removed after centrifugation. Free –SH group was assessed, in a total of 3 mL volume, by addition of 2 mL of 0.64 mL DTNB prepared in 0.2 mole phosphate buffer (pH 8) to 0.1 mL of supernatant. Absorbance at 412 nm was read on a UV- spectrophotometer. GSH was used as standard to calculate μmol –SH/g tissue.

## RESULTS

### Drug toxicity

When ginseng was injected i.p. at doses of 10, 20, 60, 600, 800 and 1200 mg/kg body weight, no mortality occurred within 24 h, showing that it was not toxic even at very high doses. To select the optimum dose, ginseng was injected i.p. at doses of 10 and 20 mg/kg body weight for 4 days. After treatment, the animals were observed for 30 days. Until day 30 no mortality or symptoms of toxicity were observed in treated mice.

### Radiation effects

Exposures of animals to a lethal dose of radiation (8 Gy) caused symptoms of radiation sickness including anorexia, epilation, weight loss, diarrhoea and lethargy. About 70% of animals died within 30 days, starting from day 4 with the maximum mortality occurring on day 13. In this group the animal weight was unchanged but the testes weight and tubular diameter decreased significantly (Table 1). Spermatogonia and spermatocytes were degenerated and their population was depleted (Table 3). High vacuolation in tubules was observed on day 7 (Fig. 2). Pyknosis was observed in a few spermatogonia and spermatocytes. The lumen was obliterated with damaged or necrotic cells. Tubules showed shrinkage and the intertubular spaces were increased. The interstitium was filled with oedematous fluid (Fig. 3).

### Combined effects of ginseng and radiation

When ginseng was administered (i.p.) at a dose of 10 and 20 mg/kg continuously for 4 days prior to irradiation, 20% and 40% mortality was observed, respectively. The animals recovered from radiation sickness within 30 days of observation.

### Animal weight

Animal weight did not exhibit significant change in any group except on day 30 in the ginseng (10 mg/kg) + radiation (8 Gy) group (Table 1).

### Testis weight

Testis remained almost the same compared with the irradiated control in the ginseng (10 mg/kg) + radiation (8 Gy) or $G_{10}$ + R group. However, a significant increase was observed on days 7, 14 and 30 in the $G_{20}$ + R group (Table 1).

### Tubular diameter

Tubular diameter did not increase in the $G_{10}$ + R group but it was increased significantly compared with the control at all the autopsy intervals in the $G_{20}$ + R group (Table 1).

**Table 1. Variation in the body weight (g) tissue weight (mg), tubular diameter (μm) of adult male Swiss albino mice after ginseng alone (G), radiation (R) and radiation + ginseng treatment (G + R)**

| Experimental group | Parameter | Autopsy intervals (days) 1 | 3 | 7 | 14 | 30 |
|---|---|---|---|---|---|---|
| $G_{10}$ | Animal weight | 17.25 ± 1.27 | 18.37 ± 1.35 | 21.04 ± 0.42 | 24.0 ± 0.51 | 26.4 ± 0.47[c] |
| | Tissue weight | 76.0 ± 1.15 | 75.0 ± 2.02 | 8.39 ± 3.64 | 85.55 ± 2.96 | 110.1 ± 3.86[c] |
| | Tubular diameter | 156.37 ± 1.60 | 158.16 ± 1.17 | 159.63 ± 1.44 | 160.27 ± 1.42 | 159.49 ± 1.45 |
| $G_{20}$ | Animal weight | 21.70 ± 0.55 | 21.30 ± 0.61 | 20.90 ± 0.50 | 20.9 ± 0.91 | 21.8 ± 1.14 |
| | Tissue weight | 96.8 ± 3.06 | 85.3 ± 3.82 | 92.3 ± 4.24 | 124.9 ± 3.82 | 89.2 ± 1.44 |
| | Tubular diameter | 165.34 ± 1.92 | 170.31 ± 4.02 | 220.02 ± 5.83 | 177.44 ± 3.58 | 183.35 ± 4.03[a] |
| R | Animal weight | 19.55 ± 0.88 | 18.95 ± 0.77 | 18.20 ± 0.85 | 17.7 ± 0.83 | 15.7 ± 0.82[c] |
| | Tissue weight | 74.4 ± 2.53 | 74.4 ± 2.13 | 59.8 ± 2.66[b] | 46.6 ± 2.59[c] | 25.9 ± 1.07[c] |
| | Tubular diameter | 145.72 ± 1.35 | 131.06 ± 3.28 | 127.56 ± 2.49 | 126.31 ± 1.91 | 126.51 ± 2.31 |
| $G_{10}$ + R | Animal weight | 17.95 ± 0.96 | 17.05 ± 1.06 | 22.60 ± 1.13[b] | 22.95 ± 1.09[c] | 22.1 ± 1.87[c] |
| | Tissue weight | 72.1 ± 1.23 | 70.0 ± 3.32 | 65.5 ± 3.36 | 46.6 ± 1.89 | 26.2 ± 2.21[c] |
| | Tubular diameter | 140.58 ± 2.33 | 135.29 ± 2.92 | 129.19 ± 2.91 | 125.32 ± 3.22 | 124.84 ± 3.17 |
| $G_{20}$ + R | Animal weight | 19.50 ± 0.66 | 20.60 ± 1.23 | 19.40 ± 0.65 | 20.10 ± 0.34 | 21.9 ± 1.24 |
| | Tissue weight | 72.1 ± 2.06 | 71.6 ± 0.90 | 82.4 ± 1.24[c] | 61.1 ± 1.89[c] | 38.3 ± 1.03[c] |
| | Tubular diameter | 187.48 ± 3.48[c] | 180.14 ± 3.81[c] | 176.39 ± 2.00[c] | 167.25 ± 2.77[c] | 177.62 ± 3.60[c] |
| Normal[d] | Animal weight | | | 21.20 ± 0.448 | | |
| | Tissue weight | | | 76.5 ± 1.021 | | |
| | Tubular diameter | | | 157.47 ± 2.90 | | |

[a] $p<0.05$ [b] $p<0.01$ [c] $p<0.001$ [d] Average number of animal weight, tissue weight and tubular diameter measured on each autopsy interval.

**Table 2. Variation in different cell counts of seminiferous tubule of the testes of adult male Swiss albino mice at various autopsy intervals in ginseng (G) only treated groups**

| Experimental group | Type of cell | Autopsy intervals (days) 1 | 3 | 7 | 14 | 30 |
|---|---|---|---|---|---|---|
| $G_{10}$ | Spermatogonia type A | 6.11 ± 0.64 | 3.44 ± 0.47 | 2.60 ± 0.22 | 9.11 ± 0.92 | 9.44 ± 0.27 |
| | Spermatogonia type B | 7.55 ± 0.59 | 7.44 ± 1.10 | 6.55 ± 1.17 | 10.50 ± 0.88 | 14.55 ± 1.81 |
| | Primary spermatocytes | 30.00 ± 1.09 | 40.00 ± 1.09 | 42.88 ± 11.42 | 46.00 ± 0.93[b] | 33.88 ± 1.39 |
| | Secondary spermatocytes | 21.44 ± 2.05 | 31.55 ± 1.92 | 30.44 ± 1.57 | 21.88 ± 1.33 | 10.55 ± 10.79 |
| | Spermatids | 21.44 ± 0.96 | 25.44 ± 1.86 | 20.88 ± 1.67 | 25.77 ± 1.13 | 10.00 ± 0.10 |
| $G_{20}$ | Spermatogonia type A | 6.40 ± 0.70 | 8.55 ± 0.79 | 7.44 ± 0.79 | 7.77 ± 0.80 | 7.00 ± 0.70 |
| | Spermatogonia type B | 8.70 ± 0.65 | 8.11 ± 0.71 | 17.55 ± 0.79 | 11.50 ± 0.86 | 13.00 ± 1.25 |
| | Primary spermatocytes | 39.20 ± 1.29[b] | 44.88 ± 0.87 | 31.44 ± 0.85 | 51.22 ± 1.18[b] | 48.22 ± 1.30[b] |
| | Secondary spermatocytes | 17.50 ± 0.79 | 19.33 ± 1.32 | 21.44 ± 1.01 | 20.00 ± 1.13 | 22.22 ± 1.38 |
| | Spermatids | 29.60 ± 1.44 | 29.33 ± 1.85 | 52.00 ± 2.81[b] | 42.55 ± 1.18[b] | 37.33 ± 1.99[a] |
| Normal[c] | Spermatogonia type A | | | 10.60 ± 0.30 | | |
| | Spermatogonia type B | | | 13.10 ± 0.79 | | |
| | Primary spermatocytes | | | 31.50 ± 1.87 | | |
| | Secondary spermatocytes | | | 47.40 ± 2.12 | | |
| | Spermatids | | | 30.00 ± 0.71 | | |

[a] $p<0.01$ [b] $p<0.001$ [c] Average number of cells counted on each autopsy interval.

## Quantitative and qualitative changes in various cell types

The following changes in the number and quality of cells were noticed in different types of cells as mentioned in Tables 2 and 3.

**Spermatogonia type A.** The irradiated group showed a significant loss in the number of testicular cells at all the autopsy intervals. However, spermatogonia type A cells in the ginseng treated animals at both the dose levels (i.e. 10 and 20 mg/kg) exhibited less radiation damage (Table 3).

**Spermatogonia type B.** In the irradiated control group significant damage was observed at all the autopsy intervals except day 30. When ginseng extract was given at a 10 mg/kg dose level, an initial increase in the number was recorded, i.e. on days 1 and 7; but this effect did not remain the same until day 30. Interestingly, the higher dose of ginseng (i.e. 20 mg/kg) could protect these cells from radiation injuries 1 week after exposure until the last day (i.e. day 30) of observation (Table 3).

Histopathological studies revealed a wide spectrum of damage in spermatogonia type A and B in irradiated control animals. Chiefly this included pyknosis, karyorhexis and exfoliation (Figs 2, 3). However, this damage was markedly reduced in the ginseng pretreated animals (Figs 4, 5).

**Primary and secondary spermatocytes.** The total number of these cells was found to be decreased in the irradiated control at all the autopsy intervals. For these cells, pretreatment at both the dose levels was found effective in improving the count (Figs 4, 5).

It was found that 10 mg/kg ginseng extract treatment could not prevent pyknosis and karyorhexis in spermatocytes. However, the 20 mg/kg dose was found to be an effective protector (Fig. 5).

**Spermatid.** The spermatid count started decreasing from day 14 onwards compared with normal animals. The 20 mg/kg dose of ginseng extract was found very effective in protecting spermatid from radiation injuries (Table 3).

Residual spermatids were observed in the irradiated group, whereas ginseng showed radioprotection thus, no such residuals could be seen in ginseng pretreated animals.

**Table 3. Variation in different cell counts of seminiferous tubule of testes of adult male Swiss albino mice at various autopsy intervals in irradiated group (R) and irradiated + ginseng treated groups (G + R)**

| Experimental group | Type of cell | Autopsy intervals (days) 1 | 3 | 7 | 14 | 30 |
|---|---|---|---|---|---|---|
| R (8 Gy) | Spermatogonia type A | 2.77 ± 0.49 | 6.00 ± 0.59 | 0.44 ± 0.22 | 4.00 ± 0.22 | 6.88 ± 0.81 |
| | Spermatogonia type B | 3.00 ± 0.33 | 5.66 ± 0.63 | 4.77 ± 0.44 | 5.33 ± 0.83 | 13.33 ± 1.27 |
| | Primary spermatocytes | 22.55 ± 0.93 | 35.44 ± 2.13 | 17.77 ± 2.13[a] | 7.00 ± 0.63[a] | 18.55 ± 1.63 |
| | Secondary spermatocytes | 12.66 ± 1.11 | 19.66 ± 1.09 | 29.33 ± 5.00[a] | 13.22 ± 1.68 | 20.66 ± 1.20 |
| | Spermatids | 45.12 ± 1.22 | 33.44 ± 2.76 | 26.44 ± 2.88 | 25.55 ± 2.51 | 0.00 ± 0.00 |
| $G_{10}$ + R | Spermatogonia type A | 5.44 ± 0.35[a] | 3.90 ± 0.76 | 5.22 ± 0.49[a] | 7.77 ± 0.75[a] | 8.56 ± 0.65 |
| | Spermatogonia type B | 6.44 ± 1.09[a] | 11.55 ± 1.17 | 18.33 ± 1.20 | 3.88 ± 0.71 | 6.89 ± 10.84 |
| | Primary spermatocytes | 24.22 ± 1.34 | 12.00 ± 0.86 | 18.88 ± 2.18 | 18.66 ± 0.74[a] | 18.89 ± 1.45 |
| | Secondary spermatocytes | 19.66 ± 3.54[a] | 28.66 ± 1.38[a] | 17.11 ± 2.26 | 12.55 ± 0.79 | 2.77 ± 0.26 |
| | Spermatids | 23.55 ± 1.20 | 36.44 ± 1.78 | 39.33 ± 3.49[a] | 26.11 ± 2.15 | 28.00 ± 1.00[a] |
| $G_{20}$ + R | Spermatogonia type A | 8.20 ± 1.03 | 6.00 ± 0.70 | 6.00 ± 0.70[a] | 17.33 ± 0.63[a] | 33.50 ± 0.45[a] |
| | Spermatogonia type B | 3.40 ± 0.49 | 14.88 ± 0.71[a] | 14.88 ± 0.71[a] | 21.11 ± 1.23[a] | 22.70 ± 0.90[a] |
| | Primary spermatocytes | 40.88 ± 0.74 | 56.00 ± 1.00[a] | 46.00 ± 1.00[a] | 22.22 ± 1.17[a] | 25.00 ± 0.80[a] |
| | Secondary spermatocytes | 27.20 ± 1.20 | 17.00 ± 0.50 | 27.00 ± 0.50 | 31.22 ± 0.93[a] | 27.44 ± 1.27[a] |
| | Spermatids | 47.50 ± 1.28 | 53.50 ± 2.37[a] | 35.00 ± 2.357[a] | 36.60 ± 0.98[a] | 48.50 ± 1.64[a] |

[a] $p<0.001$

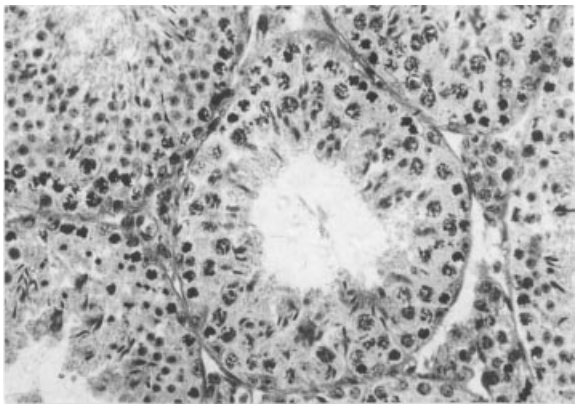

**Figure 1.** Photomicrograph of normal testis of Swiss albino mouse.

### Glutathione (GSH) level

It was noticed that liver GSH level was depleted when animals were irradiated. However, in all the ginseng pretreated groups this level was markedly raised. Interestingly, it was found that the GSH level increased in the following order: 10 < 20 < 60 mg/kg (Table 4).

## DISCUSSION

It is known that the main syndromes of acute radiation sickness are due to death of cells in critical systems of the organism such as the CNS, GI tract and haematopoietic system. The probability of a universal protection mechanism seemed very low because of the diversity and the nature of the radiation syndrome. However, on the basis of common pharmacological features of the diverse class of protectors, the idea of a common mechanism of action can be formed. It has been hypothesized that the chemicals or drugs modify or protect the organs from radiation by either scavenging the free radicals or by modulating the DNA, RNA repair or protein synthesis.

In this study two parameters were studied to evaluate the radioprotective efficacy of ginseng, namely the 30-day survival of the animals, and the cellularity of the testes after irradiation (8 Gy) and pretreatment with ginseng extract. In the present investigation it was observed that pretreatment of ginseng increased the survival time of irradiated animals by 40% to 80%. Similar results were obtained with water soluble ginseng extract against x-irradiation on mice, rats and pigs (Takeda *et al*., 1982; Yonezawa *et al*., 1981; Zhang and Chen, 1987). This increase in the survival time could be

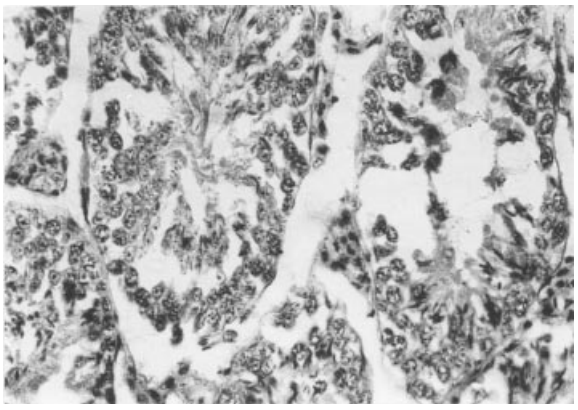

**Figure 2.** Photomicrograph of shrinkage in tubule: cytoplasmic arrest and vacuolation in irradiated group on day 7.

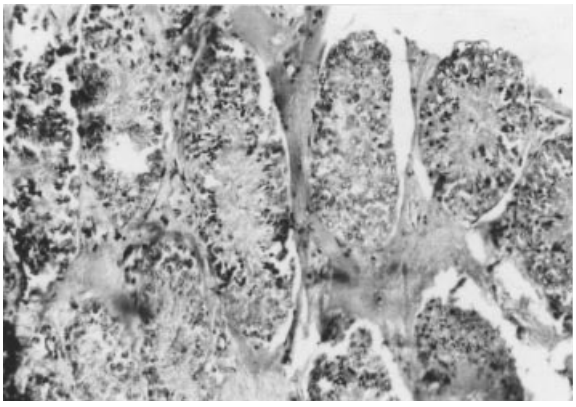

**Figure 3.** Photomicrograph of testis showing shrinkage and oedematous fluid in the interstitium group on day 14.

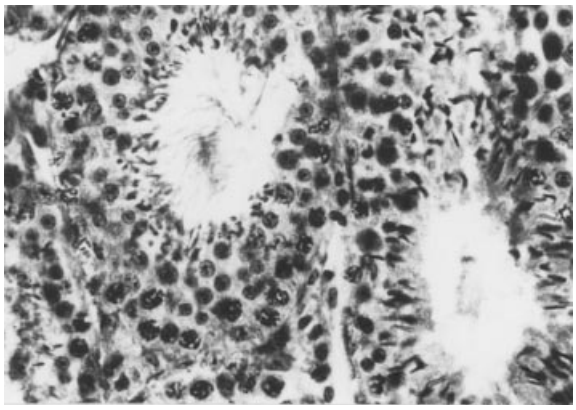

**Figure 4.** Normal cellularity of testis in the $G_{10}$+R group on day 7.

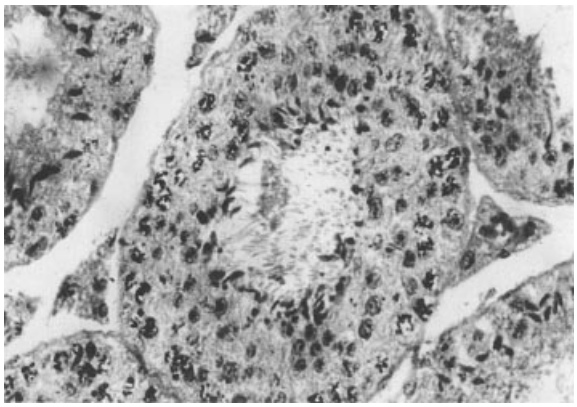

**Figure 5.** Normal histology in $G_{20}$+R group on day 7.

**Table 4. Level of glutathione (μmol/g) in liver of normal irradiated and ginseng+irradiated group**

| Experimental group | Level of glutathione (μmol/g tissue) |
|---|---|
| R | 1.94 ± 0.73 |
| $G_{10}$+R | 2.32 ± 0.35[a] |
| $G_{20}$+R | 2.61 ± 0.50[b] |
| $G_{60}$+R | 2.71 ± 0.43[c] |
| Normal | 2.11 ± 0.17 |

[a] $p<0.10$ [b] $p<0.05$ [c] $p<0.01$

because of ginseng which probably increased the number of thrombocytes and erythrocytes (Takeda, 1982). Increase in the splenic weight and splenic DNA content might also help the animals to recover from the haematopoietic syndrome (Yonezawa *et al*., 1981). Further enhancement in the survival time could be attributed to either non-specific resistance of the organism or to the normalized physiology of the animal, induced by ginseng extract (Rhee *et al*., 1991).

Ginseng extract is also found to reduce the lipid peroxidation in microsomes and mitochondria (Miyahara, 1990; Zhao, 1990). When ginsenoside (i.e. Rb and Ro) was given intravenously (i.v.) it was found to increase creatine phosphokinase and super-oxide dismutase (SOD) activities and thus reduced the lipid peroxidation. In this study the increased level of GSH and survival time can be correlated on the basis of the above hypothesis. GSH is a versatile protector and executes its radioprotective function through free radical scavenging, restoration of the damaged molecule by hydrogen donation, reduction of peroxides and maintenance of protein thiols in the reduced state (Bump and Brown, 1990).

In addition to enhancement of the life span of irradiated animals ginseng was found to protect testicular cells very effectively. This may be because of induction of DNA synthesis and repair by the ginseng extract (Rhee *et al*., 1991).

In the present investigation when ginseng was given before irradiation, the immediate mortality of the germ cells was reduced. Fewer cells of each series were affected, thus the testis cell population was significantly higher when compared with the irradiated control. Hence, recovery started much earlier than in the control because of the presence of more undamaged stem cells. However, the recovery was not complete within the experimental period. The population dynamics of spermatocytes, spermatogonia and spermatids in the ginseng pretreated group clearly showed that they were increased significantly compared with the control on day 14. It is well known that radiation causes mitotic delay and a decrease in the rate of DNA synthesis. Ginseng has been found to increase the rate of DNA synthesis (Akira *et al*., 1994) thus enhancing the recovery process and giving protection.

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