

Protective Effect of Panax Ginseng against Radiation Induced Oxidative Stress on Liver Tissue of Male Albino Rats

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ABSTRACT

Aim: The radioprotective effect of Panax ginseng extract (PGE) against oxidative stress and liver tissue injury induced by gamma radiation was investigated. Also biochemical, oxidative markers and histological changes were estimated.

Materials and methods: Twenty white albino rats weighing 120-150 g. The animals were assigned into four groups, each group contained five rats. Group (1): Animals of the first group were kept as control, group (2): Rats of the second group were given (PGE) (100mg/ kg b.w), group (3): was given (PGE) before exposure to γ - radiation (IRR), group (4): only exposed to γ - radiation (IRR). Blood samples were taken for measurement of asymmetric dimethylarginine (ADMA), lipid profile, Alanine-amino-transferase (ALT) and Aspartate-amino-transferase (AST). Tissue samples from livers were taken for determination of oxidative, nitrosative markers nitric oxide (NO_x), lipid peroxidation end product malondialdehyde (MDA), reduced glutathione (GSH) level, and superoxide dismutase (SOD) activity.

Results: In the irradiated animals, MDA and NO_x levels were significantly increased in the liver, while a marked decrease in hepatic Contents of GSH as well as the activity of SOD was demonstrated. The levels of total cholesterol, TG, LDL, as well as activities of AST, ALT, and level of ADMA, were significantly increased in the sera of the irradiated rats. This was coupled with decreased serum level of HDL. Preirradiation treatment with PGE caused significant decreases in MDA, NO_x and produced a significant elevation of GSH content, SOD activity in the liver. Moreover, a significant decrease in total cholesterol, TG, LDL coupled with increased HDL as well as the activity of AST, ALT, were significantly ameliorated when PGE was injected before irradiation but serum ADMA level was non significantly decreased

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when compared to irradiated group. Apart from these, histopathological changes also revealed the protective effect of PGE against radiation induced damage of the liver tissues.

Conclusion: The increase in oxidative stress markers and the concomitant change in antioxidant levels indicated the role of oxidative stress in radiation-induced tissue damage. Moreover, Panax ginseng extract showed a radioprotective impact against radiation induced liver damage.

Keywords: Panax ginseng extracts (PGE), γ - radiation (IRR), Asymmetric dimethylarginine (ADMA), Liver.

INTRODUCTION

Since the discovery of X-ray 100 years ago, radiation has been used increasingly in medicine and industry to help with diagnosis, treatment, and technology. Radiations have tremendous therapeutic benefits for human. However, it is also associated with the risk of serious adverse effects¹. The deleterious effects of ionizing radiation are associated with alteration in the xanthine oxidoreductase (XOR) system through the conversion of xanthine dehydrogenase (XDH) into xanthine oxidase (XO) and an increase of superoxide anion ($O_2^{\bullet-}$)². Superoxide anion can be converted spontaneously or enzymatically into hydrogen peroxide (H_2O_2) and then into the highly reactive hydroxyl radical ($\bullet OH$) that initiate the lipid peroxidation chain reaction³. Superoxide anion may also react with nitric oxide (NO) to generate the cytotoxic peroxynitrite anion ($ONOO^-$), which can react with carbon dioxide, leading to protein damage via the formation of nitrotyrosine⁴.

Exposure to ionizing radiation leads to the generation of extra reactive oxygen species and free radicals, which attack sensitive enzymes, constitutive proteins, DNA and membrane lipids⁵. Evidence of oxidative injury is proved from measurements of biochemical markers of lipid peroxidation and protein oxidation.

Lipid peroxidation is believed to be an important cause of destruction and damage to cell membranes and has been shown to be a contributing factor to the development of oxygen radicals-mediated tissue damage. However, cells are equipped with several natural enzymatic and non-enzymatic antioxidant defenses⁶. The exposure of the human body to ionizing radiation leads to depletion of these endogenous antioxidants and ultimately to the development of systemic disease⁷.

Interestingly, in 1992 it was discovered that asymmetric dimethylarginine (ADMA) plays a regulatory role in the arginine-NO pathway, by inhibiting all isoforms of the enzyme NO synthase⁸. ADMA is a methylated arginine derivative generated by the addition of methyl groups in arginine residue in proteins through protein arginine methyltransferase 1 (PRMT1), and it is secreted by proteolysis⁹. ADMA is either excreted by urine or metabolized by dimethylarginine dimethylaminohydrolase (DDAH) in the kidneys, liver, pancreas, and endothelium¹⁰ when oxidative stress is increased, ADMA levels may increase, due to a decrease in DDAH activity¹¹. An increase in PRMT1 expression is observed in parallel with increased lipid peroxidation^{12,13}. Not only oxidative stress, but also an increase in

nitrosative stress, leads to nitrosylation of DDAH enzymes and causes increased ADMA concentration¹⁴.

Many natural and synthetic compounds have been investigated for their efficacy to protect against irradiation damage¹⁵. Moreover, a potential treatment strategy for radiation exposure might be to strengthen the immune system¹⁶. Ginseng saponins are a potent antioxidant and effective to reduce tissue damage induced by free radical^{17,18}. It was reported that ginseng has a protective effect against many toxicants in human and experimental animals¹⁹, and can increase body resistance to many harmful factors and can protect tissues from damage when an organism is in stress²⁰. It reduces chromosomal aberrations induced by some chemicals²¹. Ginseng has antitumor promoting activity²² and induced radioprotective effect on skin²³, and suppression of spontaneous liver tumor formation in male mice²⁴, and could enhance the immune function of human body²⁵.

The pharmacological properties of ginseng are mainly attributed to ginseng saponins, commonly called ginsenosides, the major and bioactive constituents^{26,27}. With the development of modern chromatography, there are more 40 ginsenosides such as ginsenosides Rb1, Rb2, Rg1, Rd, and Re identified from ginseng up to date^{27,28}. Except for ginsenoside Ro and polyacetylene ginsenoside Ro belonging to oleananetype saponins, other ginsenosides are of dammarane-type saponins and classified into protopanaxadiol and protopanaxatriol groups depending on whether or not hydroxyl group at C-6 of aglycon moieties exist. Previous studies have demonstrated that ginseng has antioxidant activity as it contains ginsenosides, phenolic acids, flavonoids, and saponins. These properties of the ginseng are thought to provide many beneficial preventative effects against organ

damage²⁹⁻³¹. These findings could be interpreted as indicating that PG may possess the capacity to protect the liver from the damage induced by radiation.

This work aimed at throwing some light on the hazardous effects of γ -radiation on some biochemical parameters, as well as, histological changes in liver of adult male albino rats when exposed to γ -radiation. Moreover, the protective effect of ginseng as an antioxidant on minimizing the induced hazardous effect was a matter of concern in this investigation.

MATERIALS & METHODS

Animals

Male adult Wistar albino rats weighing 120–150 g were obtained from the Egyptian Organization for Biological Products and Vaccines (VACSERA, Giza, Egypt). Animals were kept under standard conditions and were allowed free access to a standard requirement diet and water *ad libitum*. Animals were kept under a controlled lighting condition (light: dark, 13 h: 11 h). The animals' treatment protocol has been approved by the animal care committee of the National center for radiation research and technology (NCRRT), Cairo, Egypt.

Radiation treatment

Irradiation was performed through the use of a Canadian Gamma Cell-40 (137Cs) at the National Center for Radiation Research and Technology, Cairo, Egypt. Animals were irradiated at an acute single dose level of 6 Gy delivered at a dose rate of 0.012 Gy/s.

Experimental design

Twenty white albino rats weighing 120-150 g. The animals were assigned into four groups. Each group contained five rats. Group (1): Animals of the first group were kept as control, group (2): Rats of the second group were injected interaperitoneally (i.p) with ginseng (100mg/ kg b.w), group (3):

was given ginseng (100mg/ kg b.w) before exposure to gamma radiation, a group (4): only exposed to gamma radiation.

Biochemical analysis

Animals were anaesthetized with ether, and blood samples were collected in sterile heparinized tubes by heart puncture for determination of asymmetric dimethylarginine (ADMA) was estimated using a standard enzyme linked immunosorbent assay (ELISA) method according to the manufacturer's instructions (Immundiagnostik AG, Stubenwald-Allee, Bensheim), lipid profile total cholesterol were measured using the method of Allian³², HDL cholesterol using the method of Finley *et al.*,³³ and LDL cholesterol was calculated according to Friedewald *et al.*³⁴, triglycerides determined according to the methods of Fossati³⁵. Serum liver enzymes ALT (Alanine-amino-transferase) and AST (Aspartate-amino-transferase) were estimated using the method of Reitman and Frankle³⁶.

The same animals were sacrificed by decapitation. Livers were quickly excised, washed with saline, blotted with a piece of filter paper and homogenized in ice-cold 0.15M Tris-KCl buffer (pH 7.4) to yield a 20% (w/v) homogenate using a Branson sonifier (250, VWR Scientific, Danbury, CT, USA). The homogenates were used for the determination of malondialdehyde (MDA) level and superoxide dismutase (SOD) activity, total glutathione (GSH) content, and total nitrate/nitrite (NO(x)). The homogenates were centrifuged at 800 g for 5 min at 4 °C to separate the nuclear debris. The supernatant so obtained was centrifuged (Eppendorf AG, centrifuge 5804R, Hamburg, Germany) at 15000 g for 30 min at 4 °C to get the post mitochondrial supernatant which was used to assay superoxide dismutase (SOD) activity.

Reduced glutathione (GSH) and malondialdehyde (MDA) levels in liver homogenates were determined

spectrophotometrically using the methods of Ellman³⁷ and Buege and Aust³⁸, respectively. Total nitrate/nitrite (NO(x)) was measured as the stable end product, nitrite, according to the method of Miranda *et al.*³⁹. The SOD activity was determined according to the method of Minami and Yoshikawa⁴⁰.

Histopathology

Small pieces of liver were fixed at 10% buffered formalin and embedded in paraffin. Sections of 5–6µm were cut and stained with hematoxylin and eosin before they were examined for histopathological changes under the microscope (Nikon, ECLIPSE, TS100, Japan) according to Drury and Wallington⁴¹. Images were taken with a digital camera (NIS-Elements D 2.30, SP4, Build 387) at original magnification of 200.

Statistical analysis

All the values were represented as mean ± S.D (n = 5). Students' t-test was applied for detecting the significance of difference between groups. P values of 0.05 or less were considered significant.

RESULTS

The exposure of rats to gamma irradiation induced a significant increase in the levels of serum total cholesterol, TG, LDLc. And decrease in HDLc. Compared to control group. While serum levels of serum total cholesterol, LDLc were decreased significantly and increased HDLc. On the other hand, no significant change was observed in the level of TG when the animals treated with ginseng prior to irradiation exposure compared to irradiated group (Table 1).

Gamma irradiation induced a significant increase in the levels of ALT, AST. Compared to control group while serum levels of ALT, AST were significantly decreased when the animals treated with

ginseng prior to irradiation exposure compared to irradiated group (Table 2).

Gamma irradiation induced a significant increase in the levels of MDA, NO(x) in hepatic tissues associated with a significant decrease in the GSH, SOD activity in hepatic tissues compared to control group on the other hand a significant decrease occurred in the levels of MAD, NO(x) in the hepatic tissues and a significant increase in the GSH, SOD activity in hepatic tissues when the animals treated with ginseng prior to irradiation exposure compared to irradiated group (Table 3).

In table 4 the data revealed that gamma irradiation induced a significant increase in the serum level of ADMA compared to control group. While a nonsignificant decrease in the ADMA serum level, was shown when the animals treated with ginseng prior to irradiation exposure compared to irradiated group.

Histological results of the liver

The normal histological structure of the liver was observed with normal central vein and normal hepatic lobule in Fig. (1). No pathological changes could be noticed in the liver of rats given *Panax ginseng* extract Fig. (2). The liver of the irradiated group showed focal hepatic hemorrhage in dilated central vein with vacuolar degeneration of some hepatocytes, dilated sinusoidal spaces and vacuolated hepatocytes cytoplasm Fig. (3). The liver of rats treated with *Panax ginseng* extract prior to irradiation showed some protective effects as compared to the group of rats subjected to radiation only, Showing normal architecture of hepatic cells; hepatocytes, blood sinusoids are lined by endothelial cells as well as kupffer cells. Less dilated central vein, less amount of hemorrhage and binucleated hepatocytes. Fig. (4).

DISCUSSION

Concerning lipid profile, the present investigation showed that ginseng lowered total cholesterol, triglycerides and LDL. This effect seems to be favorable since radiation resulted in an elevated lipid profile and decrease in HDL cholesterol, possibly as a result of liver injury; these changes are in agreement with previous studies carried by Feurgard *et al.*,⁴² and Agrawal *et al.*,⁴³. This could indicate that ionizing-radiation-induced oxidative stress might alter hepatic lipid metabolism and serum lipoproteins. It seems that there is an association between radiation-induced oxidative stress and elevated levels of lipid fractions and LDL-c⁴⁴. This association is similarly observed in other conditions characterized by increased oxidative stress^{45,46}. Therefore, it is suggested that oxidative stress might be an important determinant of altered lipid metabolism due to radiation exposure. The decrement induced by GE is a function of multiple integrated mechanisms including binding to PPAR α which increases β oxidation of fatty acids and consequently reduces lipid accumulation⁴⁷, inhibition of pancreatic lipase activity thereby reducing lipid digestion⁴⁸, inhibition of neuropeptide Y expression in hypothalamus⁴⁹ which is involved in stimulation of food intake, and inhibition of activity of some key enzymes involved in cholesterol and triglyceride synthesis as β methyl glutryl-CoA reductase and cholesterol 7 α hydroxylase⁵⁰. The obtained results coincide with those of Yamamoto *et al.*⁵¹, and Kim and Park⁵², who showed that ginseng reduced total cholesterol, triglycerides, LDL, but increased HDL, however the study contradicts those of Yoon *et al.*⁵³ who showed that ginseng elevated lipid profile through inhibition of PPAR α functions and Banz *et al.*⁵⁴ who showed that ginseng extract did not affect triglycerides concentration in diabetic rats. The findings of a significant depletion of cholesterol in protected rats is in corroboration with those of

Gajawat *et al.*⁵⁵ who observed that vitamin C or / and E as a protector against radiation induced increase in cholesterol.

The obtained data showed that the radiation produced alteration in biochemical parameters of the liver transaminases ALT and AST which have been widely utilized in mammalian toxicology as biomarkers of specific organ dysfunction. In general the increase in transaminases activity is usually associated with hepatocyte damage. These results are in agreement with the results recorded by Sridharan and Shyamaladevi⁵⁶ and Bhatia and Manda⁵⁷, using high-energy radiation from cobalt source. These increments in serum enzymes may be considered as a response to the oxidative stress and may be also due to the lesions occurred in liver function after its cellular damage and consequently the elaboration of its intracellular enzymes into the blood stream⁵⁸. These recorded elevations could be also due to a hypoxia state in the parenchymal liver cells and increased permeability of cell membrane⁵⁹ or mitochondrial membrane⁶⁰ causing the release of intracellular enzymes into circulation. The present investigation showed that ginseng lowered the deleterious effect of radiation on liver enzymes demonstrating the liver protecting activity of ginseng which coincides with that shown by many other investigators in-vitro and in-vivo^{61,62}. However, the present study contradicts that of Kumazawa N, *et al* 1990, who demonstrated that an intraperitoneal injection of a methanol extract of Radix Ginseng had no protective activity against carbon tetrachloride-induced hepatotoxicity in rats⁶³.

Concerning the liver antioxidant status, the current study revealed increased oxidative stress due to radiation exposure, which was evidenced by increased tissue concentration of malondaldehyde, depletion of antioxidant enzyme concentration which is

in agreement with those recorded by Koc *et al.*⁶⁴ sender *et al.*⁶⁵.

The present investigation demonstrated efficacy of ginseng extract in reversing the deleterious effect of ionizing radiation, this plant exerted its protective activity against radiation either directly by inhibiting lipid peroxidation and scavenging free radicals⁶⁶ or indirectly through enhancement of the activity of superoxide dismutase and an enzymatic free radical scavenger in the cells⁶⁷. Moreover, ginsenoside fractions have been shown to induce the cytosolic antioxidant enzyme superoxide dismutase via enhanced nuclear protein binding to its gene regulatory sequences¹⁷. According to Chang *et al.*¹⁷, the ginseng can induce the antioxidant enzymes, which are important for maintaining cell viability by lowering the level of oxygen radical generated from intracellular metabolism. The ginseng can inhibit apoptosis and suppressed hepatic necrosis⁶⁸. Ginseng extracts have been shown to scavenge reactive oxidative species (ROS) as well as attenuate lipid peroxidation⁶⁹. Our reported results concerning the decrease in lipid peroxidation and the increase in superoxide dismutase activity with ginseng agreed with those of Kim & Park⁷⁰. Previously, Geng *et al.*⁷¹ reported to attenuate hepatic TBARS by Rg1 in thioacetamide treated rats. Voces and colleagues⁷² demonstrated reduced hepatic lipid peroxidation by Panax ginseng extracts in exhaustive exercised rats. Ginseng saponins has been shown to decrease phospholipase A2 (PLA2) activity⁷³, which is responsible for lipid peroxidation⁷⁴.

Under normal conditions, the inherent defense system, including glutathione, and antioxidant enzymes protects against the oxidative damage. The concentration of intracellular GSH, therefore, is the key determinant of the extent of radiation-induced hepatic injury. The present study

demonstrated a significant reduction in GSH content following 6 Gy radiation exposures. This could be due to the enhanced utilization of the antioxidant system as an attempt to detoxify the free radicals generated by radiation. The observed increase GSH level suggests that protection by ginseng may be mediated through the modulation of cellular antioxidant levels. Thus ginseng has an important role in maintaining this crucial antioxidant in the liver and increasing the antioxidant capacity of hepatocytes. Evidence showed that ginsenoside- Rg1 can improve GSH-cycle enzymes and protect the cells from H₂O₂-induced cell death⁷⁵. Furthermore, Kwok *et al.*⁷⁶ found restored GSH levels in H₂O₂-treated endothelial cells by protopanaxatriol pretreatment. Panaxadiol ginsenosides (particularly Rb2), but not total saponins have also been found to up-regulate the transcription of other known antioxidant enzymes (superoxide dismutase and catalase) by threefold in human hepatoma cells¹⁷. Our findings demonstrated that Panax ginseng pretreatment can counter the radiation induced oxidative stress, and protects the liver cells through stabilizing GSH levels.

One possible mechanism could explain why SOD, and GSH activities dropped in the beginning was because these compounds were degraded or saturated to block radiation-induced massive free radical production, however a latent regeneration likely induced by ginseng administration would follow⁷⁷. We speculated that ginseng played an important role, particularly in amelioration of radiation-induced liver damage. Additionally, ginseng also showed the ability to prevent radiation-induced increment of hepatic MDA, suggesting that ginseng was able to inhibit lipid peroxidation and its progression in the liver. The present study demonstrated that intraperitoneal administration of ginseng played a role in reducing oxidative stress associated with radiation induced hepatotoxicity.

On the other hand, the decrease in GSH content, SOD, and the increase in MDA and total nitrate/nitrite (NO) levels in liver tissues of rats postirradiation as recorded in the present study are in agreement with those recorded by some authors⁷⁸ whole body gamma-irradiation of rats at 6 Gy enhanced the formation of NO. Similar results have been reported by Gorbunov *et al.*⁷⁹ Gamma-irradiation of rats may enhance endogenous NO biosynthesis in liver, intestine, lung, kidney, brain, spleen or heart of the animals, presumably by facilitating the entry of Ca²⁺ ions into the membrane as well as the cytosol of NO- producing cells though irradiation-induced membrane lesions. Soloviev *et al.*⁸⁰ postulated that the loss of endothelial integrity and related function in post-irradiated period is one of the most common effects of ionized irradiation. The enhancement of NO production following exposure to a high dose (6 Gy) of gamma rays was attributed to high levels of expression of the iNOS⁸¹. Zhu and Fung⁸² found that NO protects against liver injury by scavenging lipid radicals and inhibiting the lipid peroxidation chain reaction at the beginning of hepatic injury, when only a small amount of NO is being produced, NO may protect the liver through vasodilatory, antioxidative, and antiapoptotic effects. However, in the presence of massive injury (eg, high level of inducers and elevated oxidative stress), greatly increased NO production might induce the hepatocytes to progress to irreversible channel necrosis and cell death⁸³. A study demonstrated that pretreatment of Rg1 attenuated the dopamine-induced elevation of ROS or NO generation, eventually protect the mitochondria from ROS-mediated injury⁸⁴. Our findings clearly indicate that ginseng extracts offers protection against oxidative stress and maintain the stable antioxidant status.

Concerning high level of serum ADMA in irradiated group, oxidative stress

may increase the synthesis of ADMA by stimulating S-adenosylmethionine-dependent methyltransferases⁸⁵ and/or by decreasing the metabolism of ADMA by reducing the activity of DDAH⁸⁶. Carnegie *et al.*⁸⁷ indicated the potential role of the liver in the metabolism of dimethylarginines by reporting a decreased urinary excretion ratio of SDMA to ADMA in patients with chronic active hepatitis, owing to an increased output of ADMA. Tsikas *et al.*⁸⁸ reported increased concentrations of ADMA and the oxidative stress marker 15 (S)-8-iso-PGF₂ in the plasma and urine of patients with end-stage liver diseases. The level of ADMA was also found to be increased in hypercholesterolemia⁸⁹ this links ADMA with our study findings (elevated lipid profile in the irradiated group with an elevated serum ADMA level several studies have reported a correlation between ADMA and serum lipid variables⁸⁹⁻⁹¹. Also in agreement with the present study concerning radiation induced high serum ADMA, high MDA, low SOD and amelioration induced by Panax ginseng, the study carried by Yang *et al.*, demonstrated that plasma and liver ADMA levels were high in bile duct ligation (BDL) -induced cirrhotic rats, liver thiobarbituric acid reactive substances (TBARS) levels were high, and liver SOD activity was lower than the control group. In the same study, a decrease in ADMA and TBARS levels and an increase in SOD activity were observed when vitamin E was administered⁹². In another study, shown by Tain *et al.*, phenazine methosulfate and 2,3-Dimethoxy-1,4-naphthoquinone, which are H₂O₂ and superoxide donors, were put in a medium containing hepatic clone 9 cells, and PRMT1, DDAH1, and DDAH2 expression were monitored. DDAH activity decreased over time. It was shown that oxidative stress had an effect on enzyme activity in degrading ADMA rather than producing it. In the same study, melatonin prevented reduction in DDAH2 activity

induced by H₂O₂⁹³. In Yang *et al.*'s study, administration of vitamin E in 3T3-L1 adipocytes caused decreased ROS and increased DDAH activity, causing reduced ADMA concentration⁹⁴. We speculated that Ginseng extract scavenge reactive oxidative species (ROS) as well as attenuate lipid peroxidation, which may affect enzyme activity in degrading ADMA rather than producing it.

It seems that the biochemical results were justified by the histological changes occurred in the liver, where pretreatment with Panax ginseng extract offers protection against radiation damage.

CONCLUSION

It is suggested that oxidative stress is linked to the organ damage following exposure to ionizing radiation. It is hypothesized that if the oxidative stress is involved in the origin of tissue damage, then successful antioxidant treatment should delay or prevent the onset of that damage. It seems that treatment of rats with ginseng before irradiation protects against these deleterious changes. This is indicated by a significant reduction in radiation-induced hepatotoxicity because the biochemical parameters as well as the hepatic function tests are maintained within control levels. These data imply that ginseng offer radioprotection because of its powerful antioxidant activity. Our findings support scientific claims that ginseng has lipid lowering potential it might induce a hypolipidemic effect as one of action mechanism.

ADMA level is a strong predictor in liver injury also lowering serum ADMA concentrations may be a novel therapeutic target to prevent progressive liver disease.

ADMA is a biomarker that may enable us to predict risk & follow up the course of liver disease where several lines of evidence show that high ADMA levels may exert toxic effects in various cell types, thus

the clinical significance of decreasing serum ADMA is needed to further clarify the role of ADMA in the pathophysiological states of liver diseases and explore possible treatment options to improve the prognosis of patients with elevated ADMA levels.

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Table 1. Effect of whole body gamma irradiation (IRR) and administration of panax ginseng extract (PGE) on serum lipid profile triglycerides, total cholesterol, high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C)

Group Parameter	Control	PGE	IRR	PGE+IRR
S. Cholesterol (mg/dl)	70.00±1.41	69.40 ± 1.35	90.06 ±1.68***	75.50±2.75***
S. Triglyceride (mg/dl)	106.408 ± 4.88	92.42 ± 5.17**	109.04 ± 4.17	98.84 ± 8.72
S.L.D. LCholesterol (mg/dl)	21.66 ± 0.77	21.80 ± 1.72	33.18± 2.79**	25.60 ± 2.60**
S.H.D. LCholesterol (mg/dl)	40.02 ± 0.72	39.14 ± 0.85	30.08 ±1.97***	29.10 ± 1.36

Data are presented as mean ± SE, n=5 *Significantly difference **High significantly difference ***Very high significantly difference

Table 2. Effect of whole body gamma irradiation (IRR) and administration of Panax ginseng extract (PGE) on liver enzymes

Group Parameter	Control	PGE	IRR	PGE+IRR
S. ALT (U / L)	30.63 ± 0.86	27.06 ±2.48	43.24 ± 2.79***	35.12 ± 1.68**
S. AST (U / L)	53.28 ± 2.55	46.48 ± 4.42**	78.86 ± 3.08***	62.56 ± 8.45**

Data are presented as mean ± SE, n=5 *Significantly difference **High significantly difference ***Very high significantly difference

Table 3. Effect of whole body gamma irradiation (IRR) and administration of panax ginseng extract (PGE) on the oxidative, nitrosative stress biomarkers GSH, SOD, NO(x) and indices of lipid peroxidation (MDA) in liver tissues

Group Parameter	Control	PGE	IRR	PGE+IRR
Lipid peroxide content (MDA nmoles/g of tissue)	118.75±4.79	110.46±5.58**	281.10±7.46***	214.3±8.54***
GSH content (nmoles/g of tissue)	27.40±0.77	26.50±1.65	15.52±2.16***	24.52±2.83**
No level (µmoles/g of tissue)	65.26±1.40	64.38±2.65	94.26±3.83***	68.50±1.48***
SOD activity (u/g of tissue)	466.76±5.46	467.08±2.93	334.30±4.29***	457.48±6.49***

Data are presented as mean ± SE, n=5 *Significantly difference **High significantly difference ***Very high significantly difference

Table 4. Effect of whole body gamma irradiation (IRR) and panax ginseng extract (PGE) on serum level of asymmetric dimethylarginine (ADMA)

Group Parameter	Control	PGE	IRR	PGE+IRR
ADMA(µmol/L)	0.483±0.208	0.936±0.143**	1.4386±0.697*	1.2056±0.534

Data are presented as mean ± SE, n=5 *Significantly difference **High significantly difference ***Very high significantly difference

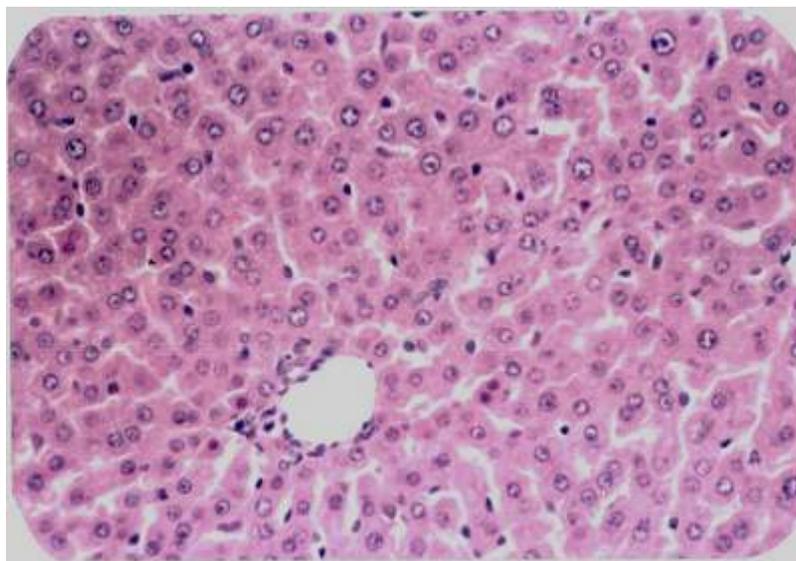


Figure 1. Section of the liver of control rat showing normal histological structure of hepatic lobules and central vein (Hx & E x200)

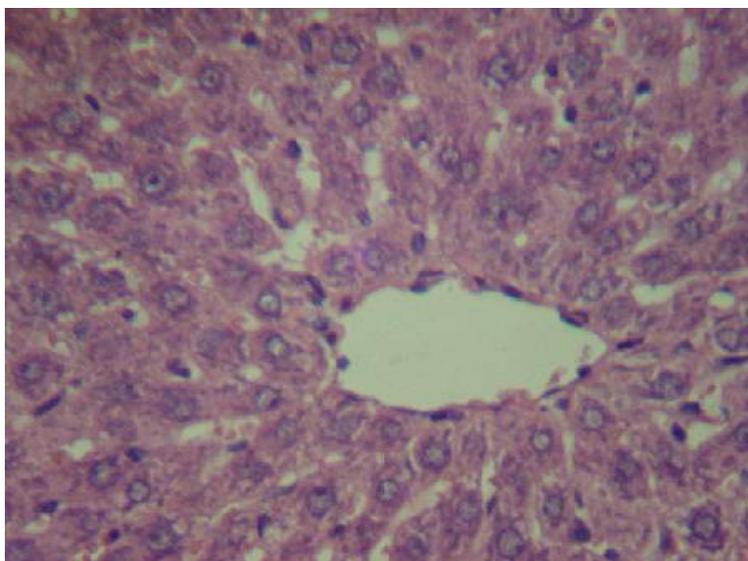


Figure 2. Section in liver of a rat treated with *ginseng* showing well developed hepatocytes, central vein with endothelial lining (→), blood sinusoids (S) and Kupffer cells (K). (Hx & E, X 200)

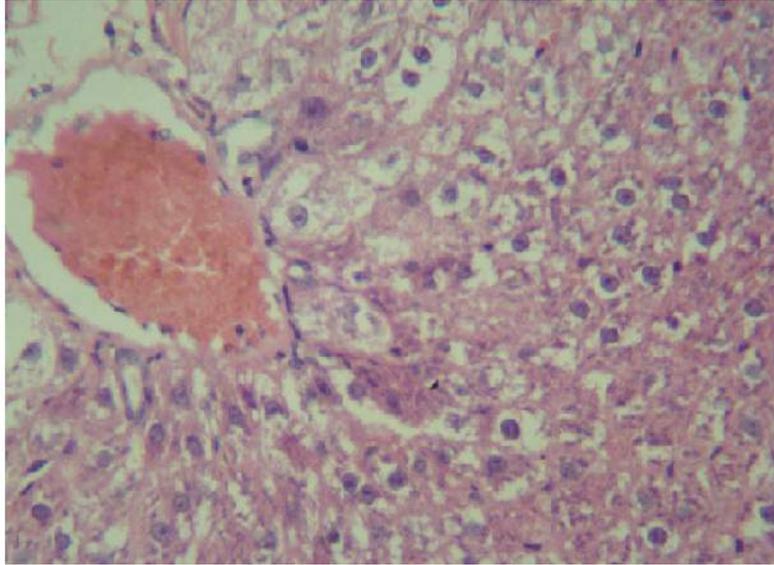


Figure 3. Showing focal hepatic hemorrhage in dilated central vein (C.V.) showing vacuolar degeneration (arrow) of same hepatocytes, dilated sinusoidal spaces (e) vacuolated hepatocytes cytoplasm (*) (H and E 200)

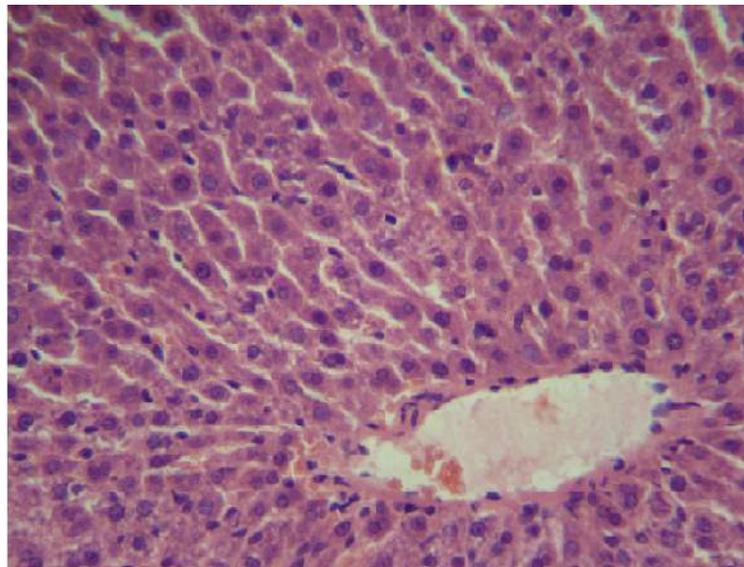


Figure 4. Showing normal architecture of hepatic cells; hepatocytes (H) .blood sinusoids (BS) are lined by endothelial cells (E) as well as kupffer cells (k). Less dilated central vein (C.V) less amount of hemorrhage and binucleated hepatocytes (*). (H and E 200)