Original Article

Anti-hepatotoxic prospect of *Panax Ginseng* extract and/or Selenium against D-galactosamine-induced liver injury in experimental rats

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Summary. The present study was performed to examine hepatoprotective effect of White *Panax Ginseng* ethanol extract (WPGE) and/or Selenium (Sel) against D-galactosamine-induced liver injury in rats. The rats received a single dose of D-Galactosamine (D-GalN) (200 mg/kg, i.p) one day before sacrifice to induce hepatotoxicity; the ethanol extract of White Panax Ginseng (240 mg/kg body weight), Selenium (0.4 mg/Kg body weight) individually and combination of (WPGE + Sel) were administered for 6 weeks. It was found that D-GalN induced hepatic damage resulted in a significant increase in the activity of AST, ALT and ALP. Results also showed that increased levels of serum cholesterol, triglycerides, low density lipoprotein (LDL-C) and very low density lipoprotein (VLDL-C) while decreased level of high density lipoprotein (HDL-C) in D-GalN induced rats. In addition the antioxidant activities such as reduced glutathione (GSH), vitamin E, superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) were decreased in D-GalN-induced rats' tissues. WPGE and Sel individually and combination (WPGE + Sel) treatments attenuated the abnormal lipid metabolism, increased oxidative stress, reduced antioxidants and also having protective activity against D-GalN induced hepatotoxicity in rats especially for the (WPGE + Sel) combined group which revealed the best results of all treatments. Thus the present study provides a scientific rationale for the traditional use of this plant extract and Sel in the management of liver diseases.

Key words: White ginseng selenium, liver injury, hepatoprotective, antioxidants, D-galactosamine (D-GalN)

«La prospettiva anti-epatotossica dell'estratto di *Panax Ginseng* e/o di Selenio sulle lesioni al fegato indotte da D-galattosamina in ratti da esperimento»

Riassunto. Il seguente studio è stato condotto per esaminare l'effetto epatoprotettivo dell'estratto in etanolo di *Panax Ginseng* bianco (WPGE) e/o Selenio (Sel) sulle lesioni al fegato indotte da D-galattosamina in ratti. I ratti hanno ricevuto una singola dose di D-Galactosamina (D-GalN) (200 mg/kg, i.p) un giorno prima del sacrificio per indurre epatotossicità; il WPGE (240 mg/kg di peso corporeo) e il Sel (0.4 mg/Kg di peso corporeo) da solo o in combinazione (WPGE + Sel) sono stati somminnistrati per 6 settimane. Si è trovato che la D-GalN ha indotto Danni epatici risultati in un significativo aumento nell'attività di AST, ALT e ALP. I risultati hanno anche mostrato che erano aumentati i livelli di colesterolo sierico, trigliceridi, lipoproteine a bassa densità (LDL-C) e lipoproteine a densità molto bassa (VLDL-C) mentre erano diminuiti i livelli di lipoproteine ad alta densità (HDL-C) in ratti indotti con D-GalN. In aggiunta l'attività antiossidante di glutatione ridotto (GSH), vitamina E, superossido dismutasi (SOD), catalasi (CAT) e glutatione perossidasi (GPx) era diminuita nei tessuti dei ratti indotti con D-GalN. I trattamenti con WPGE e Sel da soli e in combinazione (WPGE + Sel) hanno attenuato l'anormale metabolismo lipidico, aumentato lo stress ossidativo,

ridotto gli antiossidanti e hanno avuto anche un effetto protettivo sull'epatotossicità indotta nei ratti da D-GalN in particolar modo per il gruppo trattato in combinazione (WPGE + Sel) che ha dato i migliori risultati di tutti i trattamenti. Perciò il presente studio ha fornito un razionale scientifico per un utilizzo tradizionale di questo estratto vegetale e del Selenio nel trattamento delle patologie del fegato.

Parole chiave: Ginseng bianco, selenio, lesioni al fegato, epatoprotettivo, antiossidanti, D-galattosamina (D-GalN)

Introduction

Liver regeneration is an example of tissue recovery after injury. This proliferation process can be induced in experimental conditions by partial hepatectomy or by various hepatotoxic chemical agents (tetrachlormethane, D-galactosamine, thioacetamide). D-galactosamine (GalN) is well established hepatotoxicants (1). Also known for inducing the features of acute hepatitis in rats. The toxic effect of GalN is connected with an insufficiency of UDP-glucose and UDP-galactose and the loss of intracellular calcium homeostasis. These changes affect cell membranes and organelles and the synthesis of proteins and nucleic acids (2). Liver diseases is a most serious health problems in the world today but, despite tremendous advances in modern medicine, their prevention and treatment options still remain limited. Liver is the first organ to be exposed to the damaging effects of the newly formed toxic substance. Therefore, protective mechanisms relevant to the liver are of particular interest. Effectively, herbal products are widely used in the treatment of hepatic disorders all over the world (3).

Herbal medicines derived from plant extracts are being used to treat a wide variety of clinical disease (4). More attention has been paid to the protective effects of natural antioxidants against drug-induced toxicity studies especially whenever free radical generation is involved (5, 6). Dietary intake of antioxidants can inhibit or delay the oxidation of susceptible cellular substrate so prevent oxidative stress. Phenolic compounds such as flavonoids, phenolic acids, diterpenes and tannins have received much attention for their high antioxidative activity (7).

Ginseng, the root of Panax ginseng of family Araliaceae, has been used frequently in traditional Oriental medicine and is now widely used around the world (8). and generally considered to be very safe and well tolerated in animals (9). The effect of ginseng roots has been reported to differ among ginseng species, owing to differences in the quantity and composition of saponins, the main active compound in ginseng (10). Two different types of ginseng (white and red) have mainly been used in commercial. Steamed and dried (red) ginseng has been recognized as being appreciably more biologically active than simply dried (white) ginseng in some notable respects (11). Difference in biological effects of red and white ginsengs is due to the chemical changes of ginsenosides after the steaming process (12). Ginseng extract scavenges hydroxyl radicals and protects unsaturated fatty acids from oxidation, effects which may contribute to stabilizing the structure of the lipid membrane perturbed by free radical attack (13).

Selenium is an essential trace element and essential component of antioxidant enzyme glutathione peroxidase, which is acomponent of the antioxidant defense system against reactive oxygen species by synthesis of glutathione peroxidase and other antioxidant enzyme let to repairing of protein molecules (14, 15). ROS are largely generated from mitochondrial energy metabolism through oxidative phosphorylation and mostly removed by endogenous antioxidants such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) (11). Reactive oxygen species (ROS) such as superoxide, hydrogen peroxide (H_2O_2), and hydroxyl radical have been recognized to be one of the factors involved in the mechanisms of a variety of diseases including cardiovascular dysfunctions, atherosclerosis, inflammation, carcinogenesis, reperfusion injury (16). However, production of excessive oxidative stress can lead to hepatic diseases which is a major cause of illness and death in the world (17).

No studied previously the hepatoprotective effect of White Panax Ginseng ethanol extract (WGE) and/or Selenium (Sel) on D-galactosamine-induced liver injury in rats. Hence, the present study was designed to investigate the hepatoprotective effect of White Panax Ginseng methanol extract (WGE) and/or Selenium (Sel) against D-galactosamine-induced liver injury in rats.

Materials and methods

Chemicals

All the chemicals and Biochemical Kits for determinations used were of analytical grade and procured from Sigma chemicals Co., USA, Selenium as sodium selenite powder was supplied from sigma-Aldrich chemie GmbH, West Germany. Unless stated otherwise.

Preparation of white ginseng extract

Dried roots from white ginseng (WG) (Family Araliaceae) were obtained as Korean raw ginseng aged 5 years was purchased from a local ginseng center (Geumsan, Korea). WG was produced by dehydration at 60 in a dry oven. To prepare the extracts, the ginseng was crushed into powder and ultrasonicated 3 times in 10 volumes of 80% ethanol at 50 for 1 h, and then it was filtered and lyophilized. The extraction yield of WG was 36.02% according to Mi et al. (18), the residue was dissolved in saline solution (sodium chloride 0.9%) and given orally by a stomach tube after fasting for 2 hours daily for 6 weeks.

Preparation of basal diet

The basal diet was prepared using AIN-93 according to Reeves et al. (19). It consists of 20% protein (casein), 10% sucrose, 4.7% corn oil, 2% choline chloride, 1% vitamin mixture, 3.5% salt mixture and 5% fibers. The remainder was corn starch up to 100%.

Experimental animals

Fifty adult male rats of Sprague Dawley Strain weighing 180±20 gm procured from the college of pharmacy, King Saud University, KSA. and they were maintained in an air conditioned room (25±1˚C) with a 12 h light/12 h dark cycle. Feed and water were provided *ad libitum* for one week before the start of experiment for adaptation.

D-Galactosamine (D-GalN)-induced hepatotoxicity

After adaptation, rats were randomly divided into five groups of eight animals each. Group I (normal control) animals were administered a single daily dose orally with normal saline 5 ml/kg body weight. Group II was served as D-GalN treated group (positive control). Groups III-IV was given WPGE and Sel at the dose levels of (240 mg/kg body weight) and Selenium (0.4 mg/Kg body weight). Group V was given a combination (240 mg WPGE and 0.4 mg Sel /kg/body weight) 50%+50%. All these treatments were given orally daily for 6 weeks. On the last day of the treatments, the animals of groups II-V received a single dose of D-GalN in distilled water at 200 mg/kg body weight intraperitoneally after 1 h of the treatments given. Food intake was calculated daily and the body weight gain was recorded weekly (20). Feed efficiency ratio (FER): FER = weight gain (g)/ feed intake (g) was then calculated. At the end of experimental period, the animals were anesthetized by anesthetic ether the liver samples were dissected and blood was collected (21).

Liver and kidney were immediately dissected out, washed in ice-cold saline to remove the blood. Tissues were sliced into pieces and homogenized in an appropriate buffer (pH 7.0) in cold condition to give 20% homogenate (w/v). The homogenates were centrifuged at 1000 rpm for 10 min at 0˚C in cold centrifuge. The supernatants were separated and used for various biochemical estimations.

Assessment of hepatoprotective activity

The collected blood was allowed to clot and serum was separated at 2500 rpm for 15 min and the biochemical parameters like serum enzymes: aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L) (22), alkaline phosphatase (ALP, U/L) (23). Serum cholesterol was determined according to

the enzymatic method described by Allain et al. (24), serum triglycerides were colorimetrically determined according to Wahlefeld (25), the HDL-c was determined according to Albers et al. (26), while concentration of VLDL-c was estimated according to the Fridewald's equation (27).

According to (Fridewald et al. (27). low density lipoprotein cholesterol can be calculated as follows:

LDL-c = Total cholesterol – (HDL-c) – (VLDL-c).

Lipid peroxidation and non-enzymatic antioxidants biomarkers:

Liver homogenates was used for determination of tissue lipid peroxide (MDA), non enzymatic antioxidants biomarkers (GSH and Vitamin E) and enzymatic antioxidants biomarkers (SOD, CAT and GPx). Lipid peroxidation (LPO) was determined by quantifying malondialdehyde (MDA) that formed in terms of thiobarbituric acid reactive substances (TBARS) was done by the methods of Niehaus and Samuelson (28). The levels of vitamin E (29) and reduced glutathione (GSH) (30) were estimated.

Enzymatic antioxidant biomarkers

The activities of liver tissues superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) were determined calorimetrically according to Spitz and Oberley (31); Sinha (32); Paglia and Valentaine (33) respectively.

Histopathological studies

For histological studies, the liver tissues were fixed with 10% phosphate buffered neutral formalin, dehydrated in graded (50-100%) alcohol and embedded in paraffin. Thin sections (5 M) were cut and stained with routine hematoxylin and eosin stain for photo microscopic assessment. The initial examination was qualitative, with the purpose of determining histopathological lesions in liver tissue.

Statistical analysis

Data were analyzed by one-way analysis of variance followed by Duncan's Multiple Range Test (DMRT) using SPSS version 11 (SPSS, Chicago, IL). The limit of statistical significance was set at $P<0.05$.

Result and discussions

In the present study was evaluated for the hepatoprotective activity of White *Panax Ginseng* ethanol extract (WPGE) and/or Selenium (Sel) against D-galactosamine-induced liver injury in rats. Table 1 represent the D-GalN exhibited a significant reduction ($P< 0.05$) in body weight gain, feed intake and feed efficiency ratio (FER) when compared to normal control. However the individual or combined administration of either WPGE or Sel resulted in a significant elevation in the above biological changes compared to positive control. From other hand feed intake for combined group (WPGE + Sel) resulted in non significant elevation compared to normal control. In addition table (2) revealed that rats injected with D-GalN had significant ($P< 0.05$) elevates in serum levels of hepatic biomarkers as AST, ALT and ALP when compared to normal control. Meanwhile, the single or combined oral administration of either WPGE or Sel to rats suffering from liver injury exerted a marked ($P< 0.05$) re-

Table 1. Effect of WPGE and/or Sel on weight gain, feed intake and feed efficiency ratio (FER) against D-GalN-induced liver injury in rats.

Groups Parameters	Normal Control	Positive Control	WPGE (240 mg/kg)	Sel (0.4 mg/kg)	WPGE+ Sel (50% - 50%)
Weight gain (g)	82.05±6.65 a	32.32±3.21 d	56.51±6.11 c	58.41±7.13 c	69.01±8.11 b
Feed Intake (g/day)	17.94±1.26	14.64±1.21	17.90±1.31	17.67±1.21	19.86±1.25
FER	0.069±0.003 a	0.030±0.004 d	0.047±0.001 c	0.052±0.002 c	0.065±0.004 b

Values are means ± S.D n= 8 rats/group.
Values not sharing a common superscript differ significantly at p< 0.05 (DMRT)

duction in the elevated serum hepatic biomarkers activities to the normal level. D-GalN is a well-established hepatotoxicant, inducing a liver injury witch closely resembling human viral hepatitis in its morphologic and functional features and, therefore, it is very useful for evaluation of hepatoprotection. (34, 35) D-GalN has great liver specificity because hepatocytes have high levels of galactokinase and galactose-1-uridyltransferase, and it disrupts the synthesis of essential uridylate nucleotides. Depletion of these nucleotides ultimately impairs the synthesis of protein and glycoprotein, leads to progressive damage of cellular membranes resulting in a change in permeability of the cellular membrane, and finally with enzyme leakage from the cells (36). The increased levels of AST, ALT and ALP were observed in this study that may be interpreted as a result of the liver cell destruction or changes in the membrane permeability indicating the severity of hepatocellular damage induced by D-GalN, which is in accordance with previous reports (36). Treatment with WPGE (240 mg/kg body weight), Selenium (0.4 mg/Kg body weight) individually and combination of WPGE (240 mg) and Sel (0.4 mg) were attenuated the increased activities of these enzymes AST, ALT and ALP in D-GalN induced rats. Recovery towards normalization suggests that WPGE (240mg/kg body weight), Sel (0.4 mg/Kg body weight) individually and combination of (WPGE + Sel) extracts causes parenchymal cell regeneration in liver, thus protecting membrane fragility, thereby decreasing enzyme leakage. It was noticed that the combination of (WPGE + Sel) revealed the best scores of previous biomarkers when compared to D-GalN treated groups.

Table 3 represents the D-GalN induced rats had significant ($P< 0.05$) elevates in serum levels of lipid profiles as Total cholesterol (TC), Triglycerides (TG), Low density lipoprotein (LDL-C) and Very low density lipoprotein (VLDL-C) except for High density lipoprotein (HDL-C) when compared to normal control. From other hand the serum HDL–cholesterol were significantly decreased in D-GalN treated groups compared with normal control rats. Meanwhile, the single or combined oral administration of either WPGE or Sel to rats with liver injury exerted a marked (P< 0.05) reduction in the elevated serum lipid profiles to the normal level. The liver is the major site of cholesterol, bile acids and phospholipid synthesis and metabolism (37). Previously has been reported the marked alterations of lipid metabolism in D-GalN induced hepatitis in rats (38). Our results also showed that increased levels of serum cholesterol and, triglycerides, LDL-C, VLDL-C while decreased level of HDL-C

Table 2. Effect of WPGE and/or Sel on serum AST, ALT and ALP against D-GalN-induced liver injury in rats.

Groups Parameters	Normal Control	Positive Control	WPGE (240 mg/kg)	Sel (0.4 mg/kg)	WPGE+ Sel (50% - 50%)
AST (U/dl)	67.32±3.71 a	92.73±5.91 d	80.56±5.11 b	78.61±3.98 b	69.39±3.98 a
ALT (U/dl)	36.28±2.11 a	60.48±3.71 d	50.12±3.71 b	46.57±5.66 b	41.04±4.28 ab
ALP (U/dl)	32.15±2.93 a	43.27±2.51 d	36.63±2.07 b	34.71±2.65 ab	33.02±2.60 a

Values are means ± S.D n= 8 rats/group.
Values not sharing a common superscript differ significantly at p< 0.05 (DMRT)

Table 3. Effect of WPGE and/or Sel on serum lipid profiles against D-GalN-induced liver injury in rats.

Groups Parameters	Normal Control	Positive Control	WPGE (240 mg/kg)	Sel (0.4 mg/kg)	WPGE+ Sel (50% - 50%)
TC (mg/dl)	116.28±3.22 a	136.47±2.44 d	130.19±3.15 c	128.10±2.13 c	121.96±1.16 ab
TG (mg/dl)	88.48±2.12 a	122.7±3.14 d	117.83±2.52 c	109.52±2.41 b	98.90±1.90 ab
HDL (mg/dl)	61.6±2.51 a	46.37±2.81 d	50.92±3.03 d	54.25±2.27 c	57.34±1.89 a
LDL (mg/dl)	36.99±2.21 a	65.56±3.01 d	55.71±2.77 c	51.95±2.91 c	44.84±2.01 b
VLDL (mg/dl)	17.69±2.87 a	24.54±2.95 d	23.56±3.4 c	21.90±2.11 b	19.78±1.34 ab

Values are means ± S.D n= 8 rats/group.
Values not sharing a common superscript differ significantly at p< 0.05 (DMRT)

in D-GalN induced rats when compared to control. Hepatic cholesterol homeostasis is maintained by an equilibrium between the activities of hydroxy methyl glutaryl CoA (HMG-CoA) reductase and that of acyl CoA: Cholesterol acyl transferase activity on the other hand (37). The increased cholesterol level may be due to increased HMG-CoA reductase activity which is the rate limiting step in cholesterol biosynthesis (39, 40 and 41). Liver injury causes the accumulation of abnormal amounts of fats, predominantly triglycerides in the parenchymal cells. Triglyceride accumulation can be thought of as resulting from an imbalance between the rate of synthesis and the rate of release of triglycerides by the parenchymal cells into the systemic circulation (42). The elevated serum triglyceride levels observed might have been partially due to lipoprotein lipase. Treated of WPGE (240 mg) or Sel (0.4 mg) individually and combination of WPGE (240 mg) and Sel (0.4 mg) 250 in D-GalN induced rats which may be due to the extract of WPGE (240 mg) or Sel protect the abnormal activity of lipid metabolism.

Table 4 and 5 showed that intraperitoneal administration of D-GalN significantly elevated the hepatic tissue malondialdehyde (MDA) (a biochemical marker of lipid peroxidation) concentration to about 2.5-fold of the results observed in normal control. On the other hand, the non-enzymatic and enzymatic antioxidants were reduced significantly such as GSH, vitamin E, SOD, CAT and GPx status were significantly reduced in D-GalN treated groups compared to normal control. However, the single or combined oral administration of either WPGE or Sel to rats suffering from liver injury significantly restored the changes for previous parameters near the normal level. Oxidative stress has been reported as one of the major causes of D-Ga1N-induced liver damage, excessive production of free radicals resulting from oxidative stress can damage macromolecules as lipids. D-Ga1N injection increased liver MDA level while decreased GSH, vitamin E, SOD, CAT and GPx; these results were in agreement with Najmi et al. (43) and Ramesh et al. (44). In the present study showed that treatment of WPGE (240 mg) or Sel (0.4 mg) individually and combination of (WPGE + Sel) increased the liver antioxidant parameters and decreased oxidative stress which appeared in decreasing the level of MDA and increasing the GSH, vitamin E, SOD, CAT and GPx status. The reduced activities of GSH, vitamin E, SOD, CAT and GPx observed point out the hepatic damage in the rats administered with D-GalN but after the treated

Table 4. Effect of WPGE and/or Sel on liver tissues Lipid peroxidation and non-enzymatic antioxidants against D-GalN-induced liver injury in rats.

Groups Parameters	Normal Control	Positive Control	WPGE (240mg/kg)	Sel (0.4 mg/kg)	WPGE+ Sel (50% - 50%)
MDA (nmol/min/mg protein)	0.270±0.002 a	0.748±0.003 d	0.57±0.001 c	0.47±0.003 b	0.33±0.002 ab
GSH (nmol/min/mg protein)	23.3±1.25 a	10.18±1.15 d	19.09±2.71 b	19.95±2.66 b	22.35±3.28 a
Vitamin E (mmol/100 g wet tissue)	5.54 ±0.47 a	3.63±0.34 d	4.72±0.41 c	4.98±0.34 ab	5.01± 0.79 a

Values are means ± S.D n= 8 rats/group.
Values not sharing a common superscript differ significantly at p< 0.05 (DMRT)

Table 5. Effect of WPGE and/or Sel on the activity of antioxidant enzymes in liver tissues against D-GalN-induced liver injury in rats.

Groups Parameters	Normal Control	Positive Control	WPGE (240 mg/kg)	Sel (0.4 mg/kg)	WPGE+ Sel (50% - 50%)
SOD (U/mg protein)	59.07±1.25 a	32.66±1.25 d	44.90±2.71 b	52.14±2.66 b	55.63±1.28 c
CAT (nmol/min/mg protein)	0.199±0.003 a	0.144±0.002 d	0.164±0.001 b	0.173±0.002 b	0.184±0.001 c
GPx (nmol/min/mg protein)	0.63±0.02 a	0.17±0.01 d	0.37±0.003 b	0.477±0.002 b	0.57±0.001 c

Values are means ± S.D n= 8 rats/group.
Values not sharing a common superscript differ significantly at p< 0.05 (DMRT).

with WPGE (240 mg) or Sel (0.4 mg) individually and combination of (WPGE + Sel) groups showed significant increase antioxidant status and normalize the level of MDA, which indicates that the extract of WPGE and Sel having antioxidant activity. The antioxidant effects of Sel can also be due to its role in selenium-dependent thioredoxin reductase and plays an important role in functioning of the thyroid gland (45).

To verify the biochemical changes in liver, the histopathological examination of both liver for normal and D-GalN treated groups was performed. The histological observations basically support the results obtained from serum and liver tissues biochemical parameters and enzyme assays. Liver section in normal control rats showed central vein with normal histological structure of hepatic Lobule while in D-GalN treated positive control rats showing massive fatty changes with hepatocellular vacuolization as well as multifocal hepatic necrosis associated with leucocytic cells infiltration. Whereas the WGE treated rats showed hepatocellular vaculization, slight necrosis of hepatocytes associated with leucocytic cells infiltration. The liver tissues of Sel treated rats showed vacuolar degeneration of focal areas of hepatocytes. Slight vaculation of hepatocytes was showed from liver of the combination (WPGE + Sel) rats (Figs. 1-5).

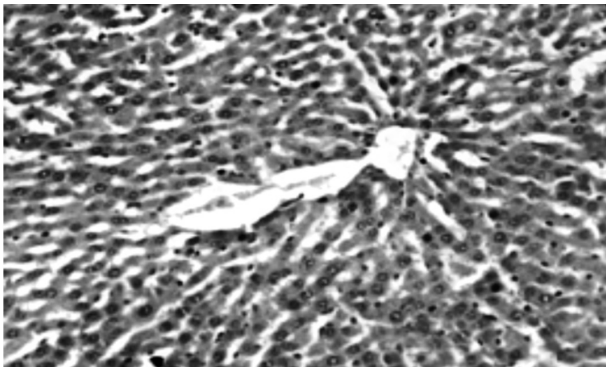

Figure 1. Liver of rat from group 1 showing the normal histological structure of hepatic Lobule (H and EX 200).

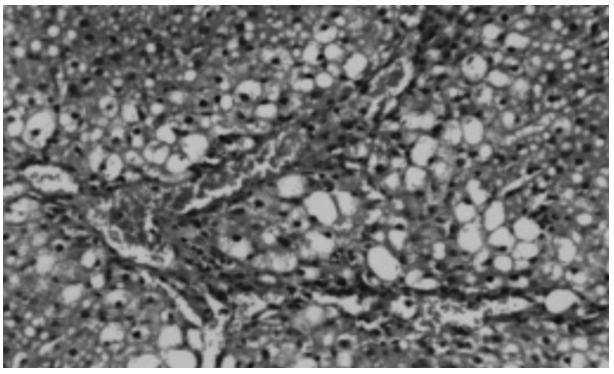

Figure 2. Liver of rat from group 2 showing hepatocellular vaculization as well as multifocal hepatic necrosis associated with cytic cells infiltration (H and EX 200).

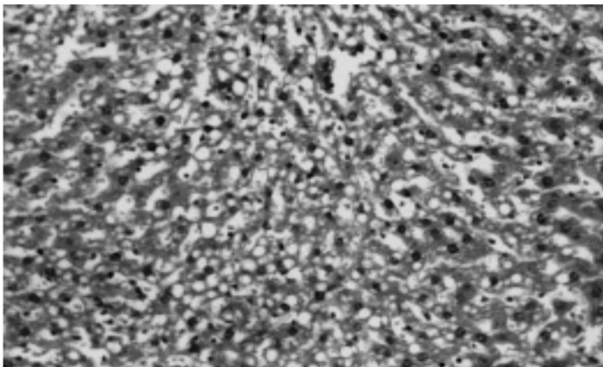

Figure 3. Liver of rat from group 3 showing hepatocellular vaculization, slight necrosis of hepatocytes associated with leucocytic cells infiltration (H and EX 200).

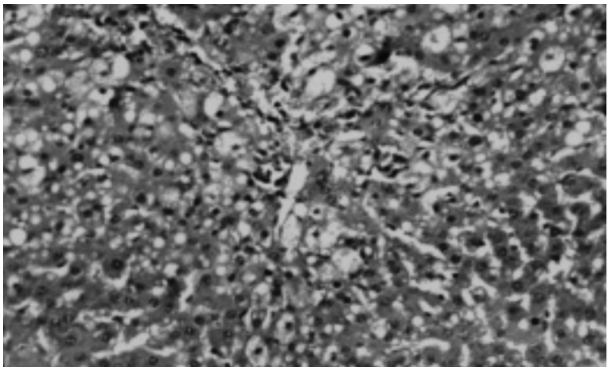

Figure 4. Liver of rat from group 4 showing vacuolar degeneration of focal areas of hepatocytes (H and EX 200).

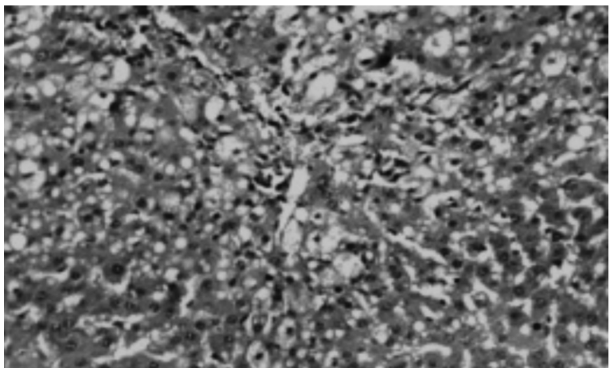

Figure 5. Liver of rat from group 5 showing slight vaculation of Hepatocytes (H and EX 200).

Conclusions

The ethanol extract of White Panax Ginseng and Selenium individually and combination of (WPGE + Sel) treatments attenuated the abnormal lipid metabolism, increased oxidative stress, reduced antioxidants and also having protective activity against D-Galactosamine induced hepatotoxicity in rats. Also it was noticed that the combination of (WPGE + Sel) revealed the best scores of all previous biomarkers when compared to D-GalN treated groups. Thus the present study provides a scientific rationale for the traditional use of this plant extract and Sel in the management of liver diseases.

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