The Egyptian Journal of Hospital Medicine Vol., 16 : 55 – 64 September 2004
I.S.S.N: 12084
1687-2002

Antihepatotoxic potential of ginseng *(Panax ginseng)* in thioacetamide-induced acute hepatocellular injury in rats

Amira Tohamey Ebrahim[1], Ahkam, M. El-Gendy[1], and Boshra El-Zawahry [2]

[1] Faculty of Science (Girls) and [2]Faculty of Medicine (Girls) Al-Azhar University, Egypt

Abstract

Previous studies demonstrated the hepatotoxicity of thioacetamide (TAA) in rats. The present study is a trial to decline TAA-hepatotoxicity by using the roots of herbal medicinal plant *(Panax ginseng)* pre-treatment .

Low dose of TAA (50-mg/kg b.wt) was chosen to induce hepatoxicity in male rats previously treated with ginseng for 10 consecutive days. The tested parameters were studied after 24, 48 and 72 hours post TAA intoxication. Fluctuatious of serum glucose were noticed in TAA intoxicated rats increased after 24 h (+ 9.31%), 48h. (+ 7.11%), followed by moderate improvement after 72 h. (+5.39%) when compared with control group. Ginseng pretreatment enhanced these changes towards the normal values.

Serum and liver enzyme activities (AST, AIT, ALP and γ GT) increased in TAA intoxicated rats which peaked after 48 h, and began to decrease after 72h. Pretreatment with ginseng improved enzyme activities to some extent.

Reduced glutathione (GSH) as well as antioxidant enzyme glutathione reductase (GSH-R) activity while lipid peroxidation (LPO) increased in TAA intoxicated rats and enhanced by pretreatment with ginseng.

This results suggest that pretreatment with ginseng could improve the detoxifying activity of the liver rats with TAA-induced acute hepatotoxicity.

Key words: Liver toxicity- Thioacetamide- Ginseng, Liver Function - Liver antioxidant - Lipid peroxidation.

Introduction

Panax ginseng (roots) are widely used for medicinal purposes, often without having been prescribed by a physician. It has been used in folk medicine against liver complaints. Ginseng is a potent antioxidant which reduce tissue damage induced by free radicals *(Sohn et al., 1993 and Kitts et al., 2000)*. It has been reported that ginseng can increase body resistance to many harmful factors and protect tissues from damage caused by stress *(Liu et al., 1995)*. Moreover, it has a beneficial effect on various hematological parameters *(Ferrando et al.,1999)*. It helped to delay experimentally-induced heart mitochondrial impairment and muscle contraction deterioration *(Tohn, 1994)*, as well as, it prevented myocardial schemia - reperfusion damage in rats *(Maffei-facino et al., 1999)*.

The most important part of ginseng is the root. The chemical constituents of this plant root are arabinose, comphore, mucilage, resin, starch and saponins *(FDA, 1999)*. The root of ginseng contains more than 18 saponins which are considered as the active fractions of ginseng. The majority of them can classified to 2 groups panaxadiol which differ in sugar moiety at the position of carbon 3-6 and 20 *(Sanada et al., 1974 and Shoji, 1974)*. The most important

ingredients in ginseng are ginsenosides. A second group compounds called panaxanes appeared to reinforce the immune system and help to keep blood sugar level under control.

Additionally, *Panax ginseng* is free from any harmful effects *(Sanada et al., 1974 and Aphale et al., l998),* also, there is no known drug interactions with ginseng *(FDA, 1999).*

Thioacetamide (TAA) is a well known hepatoxin and carcinogen. Its acute administration produces centrilobular liver necrosis. Studies on the mechanism of development of the TAA induced injury revealed that TAA is metabolized by micrsomal cytochrome P_{450} - dependent and/or, non-P_{450} dependent mixed function oxidases to toxic metabolites capable of forming irreversibly bound products with tissue macromoecules. This may initiate disturbances in hepatic cellular function resulting in cell death *(Hunter et al., 1977; Porter et al., 1979, de Ferreyra et al., l982 and Nikolaev et al., l986)* . The slowly developing cirrhosis induced by TAA has proven to be morphologically well defined and uniform, and also appears to reflect the major features of human disease *(Zimmermann et al., l987). Mangipudy et al., l995a & 1996 and Rao et al., l996)* indicated that low to moderate doses of TAA and CC14 cause hepatic necrosis but simultaneous tissue repair response stimulated in the liver leads to regression of liver injury and recovery. Studies of *Ramaiah et al. (l998)* showed that in TAA-intoxicated rats, hepatic necrosis was evident at 12 h, peaked at 36 h, persisted up to 72h and was resolved by 96h. Liver damage in hepatocytes from newly weaned rats, treated with sublethal dose of TAA, detected by the decreased levels of glutathione and protein-thiol groups (47% and 52% vs. untreated, respectively) and by enhanced malondialdhyde production (334%) Sanz *et al.* (*1998).* Previous study of *Sanz et al. (l995)* revealed that catalase and glutathion peroxidase, the two enzymes involved in the elimination of peroxides and glutathione reductase decreased significantly at the end of the 6 months of TAA-intoxication.

The objective of this study was to investigate the possible antihepatotoxic potential of ginseng in thioacetamide induced acute hepatocellular injury particularly on liver function antioxidants and lipid peroxidation.

Material and methods

Sixty four male albino rats weighting 250-275 g were included in this study, rats were divided into 8 groups each group contained 6 rats and served as follows:

Group l : Control (C) .

Group 2: (G) treated orally with *Panax ginseng* root powder in dist water (117 mg/kg) for 10 days.

Group 3: Injected ip. with (50 mg/kg) TAA and dissected after 24 h (TA24).

Group 4: Treated with (50 mg/kg) TAA (as group 3) pretreated with *Panax ginseng* (as group 2) and dissected after 24 h (G + TA24).

Group 5: Treated with (50 mg/kg) TAA (as group 3) and dissected after 48 h (TA48).

Group 6: Treated with (50 mg/kg) TAA (as group 3) and pretreated with ginseng (as group 2) and dissected after 48 h (G + TA48).

Group 7: Treated with (50 mg/kg) TAA (as group 3) and dissected after 72 h (TA72).

Group 8: Treated 50 mg/kg TAA (as group 3) and pretreated with panax ginseng (as group 2) .

The dose of panax ginseng root powder was 117 mg/kg, it was used freshly suspended in distilled water and it was given by stomach tube. Powder of panax root (aqueous extract) . Was obtained from IPECO company .

For physiological measurements, blood was collected by scarifying through jugular vein in a clean dry centrifuge tubes, kept for 30 min. at 37 °C and centrifuged at 3000 rpm for 15 min. The sera were collected in a clean Epindorf tubes and kept at -20C until analysis.

Tissue sampling:

Liver was removed and the weight was record, then homogenatated in 4

volumes of ice cold 20 m M tris HCl buffer (PH 7.2) containing 0.15 M Kcl. The homogenate was centrifuged at 3000 rpm for 10 minutes and the supernatant was immediately used for enzymatic assays.

The aspartate aminotransfrase (AST), alanine aminotransferase (AlT), γ –glutamyl transferase (γ GT), alkaline phosphatase (ALP), glucose in serum and liver fresh tissue (AST), liver fresh tissue (ALT), and liver fresh tissue (ALP) were measured biochemically using test kits of Stanbio .Serum (AST) and (ALT) were determined according to *Reitman and Frenkel (l957)*. Serum (ALP) activity was determined according to *Moss (l984)* γ -glutamyltransferase (γ -GT) was determined according *Persijn and Vander Slik (l976)* . Glucose was detected by using glucose oxidase according to *Howanitz and Howanitz (l984)* . Natural liver antioxidant glutathione, (GSH) content was determine according *Prins and Loose (l969)* and glutathione reductase (GSSGR) activity was determined by the method *Beutler (l975)*. Lipid peroxidation (Lpo) product (MDA) was estimated according to *Stroev and Makarova (l988).*

Results

As shown in table (1) serum glucose in TAA intoxicated groups increased significantly after 24 h, (+9.31%), 48 h (+7.11%) & 72 h (+5.39%). Ginseng alone has insignificant decreased on serum glucose. Mean while ginseng pretreatement in TAA intoxicated rats improved serum glucose at different intervals 24 , 48 and 72 hours.

Serum and liver enzyme AST, ALT, γ-GT and AIP activities were estimated as markers of liver function (Table 1 & 2). TAA intoxicated rats showed high significant increases in these enzymes activities after 24, 48 and 72 hours. Ginseng pretreatment slightly improved the dengerous effect of TAA on the activities of the studied enzymes. Ginseng alone slightly decreased the activities of serum AST, ALT, AIP and γ-GT (Tables 1 & 2) when compared with control (Tables 1 & 2).

GSH in TAA intoxicated groups in (Table 3) slightly decreased at 24 h (-63.02%) 48 h (-56.77%) and72 h. (-48.59%),GSHR activity reduced significantly at 24 h., 48 and 72 h (-10.69, -40.77 & -42.98%) respectively. On the otherhand LPO was stimulated by TAA intoxication and increased significantly after 24, 48 and 72 h.(+23.01 %, + 21.40 % & 20.70%) respectively.

Ginseng pretreatment in TAA- intoxicated rats enhanced the liver contents of GSH & LPO as well as the activities of GSH-R (Table 3).

Ginseng alone has no effect on both GSH & LPO and GSH-R activity when compared with control group (Table 3).

Table (1): Serum glucose (mg/l00 ml), AST, AIT, AIP and γ-GT (u/L) activities in control (C) , ginseng (G) and thioacetamide (TA) at different time intervals (24, 48 and 72 hrs)

	C	G	TA 24	G + TA24	TA 48	G + TA 48	TA 72	G + TA 72
Glucose (mg/100ml) % of change	93.42±2.22	92.20±2.33 -1.30	102.12±2.75* +9.31	97.12±2.64* +3.96	100.07±2.50* +7.11	95.97±3.29* +2.73	98.46±2.61* +5.39	94.01±3.29* +0.63
Serum AST(u/L) % of change	13.60±0.68	13.40±1.39 -1.47	22.20±1.04* +63.23	15.20±0.92* +11.76	17.60±0.68* + 29.41	15.00±0.84* + 10.29	16.61±1.12* + 22.13	14.80 ± 0.73* + 8.82
Serum AIT(u/L) % of change	14.80±0.81	14.04± 1.17 -5.13	23.60 ± 1.43* + 59.45	19.41 ±1.03* + 31.14	20.61 ±0.20* +39.25	18.20±0.58* + 22.97	19.01±0.75* + 28.44	16.00±0.63* +8.11
Serum AIP(u/L) % of change	54.22±2.58	54.10± 5.13 - 0.22	72.66±3.60* + 34.01	69.06±2.55* + 27.36	70.04±4.47* + 31.02	62.71±1.73* + 15.65	67.91±4.33* + 25.24	58.10±2.59* + 7.15
Serum γ-GT(u/L) % of change	1.38±0.29	1.27± 0.30 -7.97	3.38±0.36* + 144.92	2.6±0.38* + 88.41	3.96±0.37* + 186.95	3.28±0.43* + 137.68	2.94±0.37* +113.04	2.48±0.31* + 79.71

-All values represent the mean ±SE of 6 animals.
* Significant at P<0.05

Table (2): Liver fresh tissue AST, AIT and AIP (u/100 g) activities in control (C) , ginseng (G) and thioacetamide (TA) at different time intervals (24,48 & 72 hrs).

	C	G	TA 24	G + TA 24	TA 48	G + TA 48	TA 72	G + TA 72
Liver AST u/100 g % of change	14.74±1.34	14.21±1.16* -3.59	41.6.0 ±2.22* +182.22	36.40 ±1.78* + 146.94	37.90 ±4.78* + 157.12	29.90 ±2.69* + 102. 84	30.24 ±3.51* + 105.15	19.98 ± 1.21* + 35.54
Liver AIT u/100g % of change	502.10±33.72	497.02± 48.88* - 1..01	671.67 ± 33.29* + 33.77	596.71 ±24.95* + 18.84	660.98 ±42.60* + 31.64	579.38 ±49.23* + 15.39	646.98 ±49.95* + 28.85	558.14±10.70* + 11.16
Liver AIP u/100 g % of change	299.08±41.59	291.14 ± 38.41* - 2.65	399.06 ±20.07* +30.41	374.26 ±72.89* + 25.13	343.40 ±21.86* + 14.81	352.90 ±10.26* + 17.99	337.78±27.24* +12.93	329.21±18.13* +10.07

- All values represent the mean ± SE of 6 animals .
* Significant at P <0.05

Table (3): Liver glutathion (GSH) mg/g wet. Tissue , glutathion reductase (GSSGR) mg/g wet. Tissue and lipid peroxidation (LPO) /n mol/g wet. Tissue in control (C) , ginseng (G) and thioacetamide (TA) at different time intervals (24, 48 & 72 hrs)

	C	G	TA 24	G +TA 24	TA 48	G+ TA 48	TA 72	G + TA 72
GSH Mg/g wet. Tissue) % of change	3.84. ±0.32	3.71±0.15 - 3.39	1.42 ±0.20* - 63.02	2.01 ±0.37* -47.65	1.66 ±0.28* -56.77	2.79 ±0.35* -27.34	1.96 ±0.27* -48.59	2.93± 0.16* -23.69
GSHR (u/g wet) % of change	10390.24±180 .78	10386.90± 250.32 -0.03	9279.00 ± 367.35* -10.69	9431.50 ±296.87* -9.23	6153.83 ±641.08* -40.77	9621.17 ±600.81* -7.40	5923.50 ±722.99* -42.98	10292.17±560 .05* -1.90
LPO (n mol/g wet. Tissue) % of change	9.95±0.50	9.81 ± 0.49 -1.40	12.24 ±0.59* + 23.01	11.02 ±1.09* + 10.75	12.08 ±0.32* + 21 .40	10.72 ±0.38* +7.73	12.01±0.57* +20.70	10.36±0.32* +4.12

-All values represent the mean ± SE of 6 animals .
* Significant at P<0.05

Discussion

The toxic effects of TAA may generally attributed to its selective nuclear oxidative damage *(Clawson et al., l997)*, decreases in total liver protein and liver microsomal protein *(Cascales et al., l991)* , as well as decreases in serum albumin concentration .The administration of thioac-etamide in rats induces nodular cirrhosis of the liver, characterized by fibrous septae, parenchymal nodules, prolfieration of the bile ducts and changes in lipid metabolism *(Torres et al., l997)*.

The formation of free radicals and cytotoxic oxygen metabolites probably play a key role in various types of tissue degeneration and pathology such as aging, cancer and retinal degeneration *(Brown, l995)*. In order to overcome the effect of free radicals and to reduce the damaging effect of oxidants, a variety of pharmacological antioxidants such as - glutatione, cellulopl-asmin and transferrin have examined *(Gutteridge, l986)*. In our study, we attempt to investigate the effect of *Panax ginseng* (ginseng) root to modulate the hepatotoxic effect induced by thioacetamide in adult male albino rats.

TAA-toxicity led to an elevation of serum glucose after 24 h. Followed by significant reduction after 48 h. and begn to return towards the normal level after 72 h. This effect may be attributed to transient effect of TAA on liver glycogen producing glycogenolysis at first. The increased glucose also, may effect pancreatic B-cell and insulin secretion, which followed by enhancement effect after 72 h. Similar results were obtained by other drugs such acetomenophane. Two hours following a hepatotoxic dose, hepatic glycogen was depleted and this was accompanied by a marked increase in serum glucose *(Hinson et al., l983)*. Subsequently dramatic increase, in serum insulin were observed. Serum glucose levels showed an inverse correlation to serum insulin levels followed by decreased serum glucose levels *(Hinson et al., l984)*.

Treatment with ginseng prior to TAA administration produced prophylactic effect against TAA toxicity on liver and pancreas and could counteract the fluctuations of serum glucose level. Different mechanisms may be involved in lowering blood level by ginseng in TAA intoxicated rats after 24 h., Saponin content in ginseng could stimulate glucose uptake by erythrocytes *(Hasegawa et al., l994)*. Ginseng contains insulin-like substances which inhibited epinephrine-

induced lipolysis and stimulated lipogensis from glucose in fat cells *(Takaku et al., l990)*. Finally ginseng inhibited absorption of glucose or maltose in small intestine and increased duodenal muscle movement *(Onomura et al., l999)*.

Regarding liver enzymes, transaminase activities were measured since they are indicators of liver damage, and γ-GT increased in drug liver toxicity . Acute liver diseases manely increased serum transaminases. The elevations of the activities of the studies enzymes were attributed to damage effect of TAA on liver tissue.

The administration of TAA in rats induced liver injury characterized by significant elevations of the activities of enzymes AST, AIT, AIP and γ -GT. These results are in agreement with *(Osada et al., l986, l988) and Zimmernann et al., l986 and l987)* . They observed on increases in both serum transaminases 72 h. after TAA administration in rats. *Nozu et al. (1992)* detected increase γ-GT in rats treated with TAA administration in drinking water for 3 months. The results were obtained by *(Cascales et al., l991, Kretzschmar et al., 1991 , Fontana, l996 and Fontana et al., l996)* recorded significant increases of AIP and γ-GT activities in the serum of TAA treated rats suggesting an altered glutathione synthesis and export.

Improved enzyme activities (AST, AIT, AIP and γ -GT) in TAA-intoxicated rats pretreated with ginseng may be due to the antioxidant activity of ginseng. These results are confirmed by the results of *Zuin et al. (1987)* who found that ginseng reduced γ-glutamyl transpeptidase levels in elderly patients after 6 and 12 weeks of treatments while transaminases were slightly, but not significantly lower after ginseng treatment for 6 and 12 weeks. Also, *Hinko et al. (l985)* found that hepatocytes exposed in vitro to an extract of ginsenosides from the roots of *Panax ginseng*, had an anti-hepatotoxic effect.

Glutathione (GSH) is central to the antioxidant defense system of the cell by reducing hydrogen peroxide *(Meister, 1992)*. Although GSH decreased insignificantly in rats intoxicated with TAA, this decrease may be due to the inhibition of glutathione reductase (GSH-R) activity. GSHR is responsible for the reduction of oxidized glutathione (GSSG) to reduced glutathione (GSH). GSH-R posses a critical sulphydril group at its active site which participates in the reduction of GSSG *(Gerson and Shaikh, l984)*.

The present results indicated that pretreatment with ginseng improved the liver contents of GSH and the activities of GSH-R in TAA intoxicated rats at different tested intervals. The increased activity of GSH-R is required to maintain sufficient content of GSH which exerts on antioxidant property and lowers free radicals damaging effect *(Whanger, l992)* . The protective effect of *Parnax ginseng* root has been examined in human *(Yun and Choi, l998 and Lee et al., 2002)*, rat *(Xiaoguang et al.,1998 and Nehal and Amira 2002)* and mice *(Yun et al., 1996)*. They all deduced that *Panax ginseng* root has a potent therapeutic activity and could enhance immune function.

In addition to the reduction of liver GSH content and activity of GSH-R, there was also an increase of liver lipid peroxidation in TAA-intoxicated rats after 24, 48 and 72 h. when compared with control group., These results indicated that GSH depletion and LPO elevation (oxidative stress) could play an indirect role in the hepatotoxicity of TAA. This evidence is supported by *Dyroff and Neal (l981)* who reported that reactive intermediates by TAA (thioacetamide sulfoxide and sulfone) are involved in the initiation of liver injury.

The present data showed that ginseng had a protective effect against TAA toxicity. The possible mechanisms would be firstly: the antioxidative properties of its ginsenoside compounds, since the effect of ginseng as an antioxidant agent are well known and its effect as a protective agent against lipid peroxidation in the liver and brain have been reported *(Lee et al., l995 and Xiaoguang et al.,l998*). *Zhang et al. (l996*) detected the stabilization of lipid structures against attack by free radicals as a result of ginseng intake. Likewise, it has been shown that the saponins contained in ginseng cause transcription of the superoxide dismutase gene (Cu-Zn-SOD) mediated by the transcription

factor AP2 *(Kim et al., 1996)*. Additionally, it has been reported that ginseng administration could increase the hepatic glutathione peroxidase activity and could reduce glutathione level in liver *(Voces et al.,l999)*. Superoxide dismutase and glutathione peroxidase are the most important antioxidant enzymes in the antioxidant defense system. The second mechanism involves:a) Stimulating effect on DNA repair synthesis (*Rhee et al.,l990)*, b) Inhibitory effect on mutagenicity *(Rhee et al., l990)* , c) stimulating effect on protein and RNA synthesis *(Yokozawa et al.,l996)* d) stimulating effect on cell-immune system *(Shin et al., 2000)*. Also, *Bae and Lee (2004)* suggested that the inhibitory effect of ginseng on the formation of glycated hemoglobin could be attributed to the antioxidative activity of ginseng.

From our present data it can be concluded that alteration of liver function and oxidation status by TAA intoxication could be improved in rats pretreated with ginseng.

References:

1. **Aphale, A.A.; Chhiba, A.D.; Kumbhakarna, N.R.: Mateanuddin, M. and Dahat, S.H. (l998):** Subacute toxicity study of the combiation of ginseng (*Panax ginseng*) and ashwagandha (Withania Somnifera) in rats: a safety assessment. Ind. J. Physiol. Phafrmacol. 24 (2) 299-502.
2. **Bae, J.W., and Lee, M. H. (2004):** Effect and putative mechanism of action of ginseng on the formation of glycated hemoglobin in vitro. J. Ethno. Pharm. 91 (1): 137-40.
3. **Beutler, E. (l975):** Red-cell metablism, a manual of biochemical methods 2nd edi. Pub. Grune and Stration, New. York , 69-70.
4. **Brown, R.H. (l995):** Amylotrophic lateral sclerosis : recent insights from genetics and transgenic mice. Cell: 80 , 687-692.
5. **Cascales, M.; Martin, Sanz, P.; Craciunescu, D.G. and cascales, C. (l991):** Alterations in hepatic peroxidation mechanisms in thioacetamide induced tumors in rats. Effect of a rhodium (III) complex. Carcino, 12: 233-240.
6. **Clawson, A.G.; Catharine, M.; Benedict, M.; Mark, R.K. and Judith, W. (l997):** Focal nuclear hepatocyte response to oxidative damage following low dose thioacetamide intoxication. Carcino: 18 (8): 1663-1668.
7. **De-Ferryra, E.C.; de-fenos, O.M. and Castro, J.A. (l980):** Effect of different chemicals on thioacetamide-induced liver necrosis . Toxicology, 16: 205.
8. **Dyroff, M.C. and Neal, R.A. (l981):** Identification of the major protein adduct formed in rat liver after thioacetamide administration. Cancer Res. 41: 4430-3435.
9. **Ferrando, A.; Vila, I.; Voces, J.A.; Cabral, A.C.;Alvarez, A.I. and Prietog, J.G. (l999):** Effects of gineseng extract on virious hematological parmaeters during aerobic exercise in the rat. Planta-Medica 65: 288-290.
10. **Fontana, L.; Moreiva, E.; Isabel, M.T. and Rios, A. (l996):** Serum amino acid changes in rats with thioacetamide-induced liver cirrhosis. Toxcol. 106:197-206.
11. **Food and drug administration: Copyright (l999):** Medical Economics Company, Inc. Health privacy Policy.
12. **Gerson, R.J. and Shaikh, Z.A. (l984):** Differences in hepatic uptake of cadmium and mercury by the rat hepatocyte primary cultures. Role of sulphydryl carrier. Biochem, pharmacol., 33: 199-203.
13. **Gutteridge, J.M.C. (l986):** Antioxidant properties of the proteins ceruloplasmin, albumin and transferrin. A study of their activity in serum and synovial from patients rheumatoid arthritis . Biochem. Biophys. Acta: 119-127.
14. **Hasegawa, H.; Matsumiya, S.; Murakami, C.; Kurokawa, T., Kasai, R.; Ishibashi, S. and Yamasaki, K. (l994):** Interactions of ginseng extract, ginseng separated fractions and some triterpenoid saponins with glucose transporters in sheep erythrocytes. Planta Med. 60 (2) : 153-157.
15. **Hikino, H.; Kiso, Y.; Kinouchi, J. et al. (l985):** Antihepatotoxic effects of ginsenosides from *Panax ginseng* roots. Planta Med. 1: 62-64.
16. **Hinson, J.A.; Mays, J.B. and Cameron , A.M. (l983):** A cetaminophan induced hepatic glycogen depletian and hyperglycemia in mice. Biochem. Pharmacol. 32: 1979-1988.
17. **Hinson, J.A.; Han-Hsu, H.; Mays, J.B.; Holt, S.J.; MClean, P. and Ketterer, B. (l984):** Acetomenophan-induced alterations in blood glucose and blood insulin levels in mice . Res. Comm. Chem. Path. Pharmacol. 43: 381-391.
18. **Howanitz, P.J. and Howanitz, J.H. (l984):** In clinical diagnosis and management by

laboratory methods, 17th ed., T.B. Henry Ed., W.B. Saunders Philadelphia, P: 168.

19. **Hunter, A.L.; Holscher, H.A. and Neal, R.A.(l977):** Thioacetamide induced hepatic necrosis. I. Involvement of the mixed function oxidase enzyme system. J. Pharmacol. Exp. Ther., 200-439.
20. **Kim, V.; Park , K. and Rho, H. (l996):** Transcriptional activationof the Cu & Zn. Superoxide dismutase gene through the AP2 site by ginsenoside Rb2 extracted from a medicinal plant panax ginseng. J. Biol. Chem., 2H (40) : 24539-43.
21. **Kitts, D.D.; Wijewickreme, A.N. and Hu, C. (2000):** Antioxidant properties of a North America ginseng extract. Mol. Cell, Biochem. 203 (1-2): 1-10.
22. **Kretzschmar, M.; Machnik,G;Mullers, A.; Splinter, F.K. and Zimmermann,T. (l991):** Gamma glutamyl transpeptidase in experim-ental liver cirrhosis induced by thioacet-amide: a biochemical and enzyme histoc-hemical study. Exp. Pathol 42, 195-203.
23. **Lee, D.W.; Sohn, H.O.; Lim, H.B.; Lee, Y.G.; Aprikian, A.G. and Aprikian, G.V. (l995):** Antioxidant action of ginseng an hypothesis . Korean J. Sci. 19: 31-38.
24. **Lee,H.C.; Hwang, S.G.; Lee, Y.G.; Sohn, H.O.; Lee, D.W.; Hwang, S.Y. and Moon, J.J. (2002):** In vivo effects of *Panax ginseng* extracts on the cytochrome P450 dependent mono-oxygenase system in the liver of 2,3,7,8, tetrachloro dibenzo-P-dioxin-Xposed guin pig. Life-science, 71 (7): 757-769
25. **Liu, J.; Wang, S.; Lium, H.; Yang, L. and Nan, G. (l995):** Stimulating effect of saponin from *Panax ginseng* on immune function of lymphocytes in the elderly. Mech. Ageing Dev., 83(1): 43-53..
26. **Maffei-Facino, R.; Carini, M.; Aldini, G.; Berti, F. and Rossoni , G. (l999):** Panax ginseng administration prevents myocardial ischemia-reperfusion damage induced by hyper baric oxygen evidence an antioxidant. Planta Medica : 65 (7): 614-619.
27. **Mangipudy, R.S.; Chanda, S. and Mehendale, H.M. (l995a):** Hepatocellular regeneration: Key to thioacetamide autopro-tection. Pharmacol. Toxicol.: 77 (3): 182-8.
28. **Mangipudy, R.S.; Chanda, S. and Mehendale, H.M. (l995b):** Tissue repair as a response to thioacetamide hepatotoxicity . Environ.Helth Perspect. 103, 260-267.
29. **.Mangipudy, R.S.; Rao, P.S. and Mehendale,H.M.(l996):** Effect of colchacine antimitosis on thioacetamide hepatotoxicity. Environ. Health Perspect. 104, 744-749.
30. **Meister, A. (l992):** Commentary on the antioxidant effects of ascorbic acid and glutathione. Biochem. Pharmacol., 44: 1905-1915.
31. **Moss, D.W. (l984):** In the methods of enzymatic analysis, ed., Hu. Berg meyer Verlag-Chemie, 3rd edition, V4 , 92-106.
32. **Nehal, A.M. and Amera, T. (2002):** Ginsing pre-treatment lessens the acute testis injury of rats induced by thioacetamide. Egyptian. J. of Hospit. Med.; 9: 28-47.
33. **Nikolaev, V.; Kerimova, M.; Naydenova, E.; Dimov,S.;Savov,G.and Ivanov, E. (l986):**The effect of thioacetamide on rat liver plasma membrane enzymes and its pot-entiation by fasting . Toxol. 38 : (203-208).
34. **Nozu, F.; Takeyama, N. and Tanaka, T. (l992):** Changes of hepatic fatty acid metabolism produced by chronic thioacetamide administration in rats. Hepatology, 15: 1099-1106.
35. **Onomura, M.; Tsukada, H.; Fukuda, K.; Hosokawa, M.; Nakamura, H.; Kodama, M.; Okya, M. and Seino, M. (l999):** Effects of ginseng radix on sugar absorption in the small intestine. Am.J. Clin. Med . 27 (3-4); 347-354.
36. **Osada, J.; Aylagas, H.; Sanchez-vegaza, I.; Gea, T.; Millan and Palacios, E. (l986):** Effect of S-A denosyl-Lmethionine thioace-tamide-induced liver damage in rats. Toxicol. Lett, 32 : 97-106.
37. **Osada, J.; Aylagas, H.; Mirobradors, M.J. and Palacios -Alaiz, E. (l988):** Lysopho-sphatidylclastine is implicated in thioacet-amide induced liver necroses. Biochem. Biophys. Res. Commun., 154: 803-808.
38. **Persijn, J.P. and Van der slik, W. (l976):** Colorimetric method for the determination of serum L-Y -glutamyltransferase J. Clin. Chem. Clin. Biochem. 14: 421.
39. **Porter, W.R.; Gudzinovicz, M.J. and Neal, R.A. (l979):** Thioacetamide induced hepatic necrosis II. Pharmacokinetics of thioacetamide and thioacetamide S. oxide in the rat. J. Pharmacol. Exp. Ther., 208-386.
40. **Prins, H.K. and Loose3, J.A.(l969):** Glutathione "chapter 4" biochemical methods in red cell,. Genetics. Edited by J. Yanis. Academic Press, N.Y. D. London: 126-129.
41. **Ramaiah, S.K.; Soni, M.G.; Bucci, T.J. and Mehendale, H. M. (l998):** Diet restric-tion enhances compensatory liver tissue repair and survival following administration of lethal dose of thioacetamide. Toxicol. Appl. Phamacol. 150 (1): 12-21.
42. **Rao, P.S.; Dalu, A.; Kulkarni, S.G. and Methendale,H.M.(l996):**Tissue regeneration

prevents lethality in iso propanol potentiated carbon teterachloride hepatotoxicity. Toxicol. Appl. Pharmacol. 140 (2), 235-244.

43. **Reitman, A. and Frankel, S. (l9957):** Colorimetric method for the determination of serum glutamic oxaloacetic and glutamic pyrevic transaminases. J. Clin. Path. 28-56.
44. **Rhee, Y.H.; Ahn, J. Choe J.; Kang, K.W. and Joe, C. (l990):** Inhibiton of mutgenesis and transformation by root extract of Panax ginseng in vitro. Planta. Med. 57: 125-128.
45. **Sanada, S.; Kondo, N.; Shoji, J.; Tanaka, O.; and Shibata, S. (l974):** Studies on the saponins of ginseng. 1-structures of ginsenoside-Ro, Rb1, Rb 2 Rc and Rd. Biol. Pharm. Bul. 22: 421-428.
46. **Sanz, N.; Diez-Fernandez, C.; Fernandez-Simon, L.; Alvarez, A. and Cascales, M. (l995):** Relation between antioxidant systems, intracellular thiols and DNA ploidy in liver of rats during experimental cirrhogenesis. Carcin. 16 (7) : 1585-93 .
47. **Sanz, N.; Diez-ferrandez, C.; Fernandez-Simon, L.; Alvarez, A. and Cascales, M. (l998):** Necrogenic and regnerative responses of liver of newly weaned rats against a sublethal dose of thioacetamide. Biochem. Biophy. Acta. 23: 1384 (1): 66-78.
48. **Shin H. R.; Kin, J.; Yum, T.K.; Morgan, G. and Vainio, H. (2000):** The cancer preventive potential of panax ginseng a review of human and experimental evidence . Cancer causes control. 11 (6): 565-567.
49. **Shohn, H.O.; Lim, H.b.; Lee, Y.G.; Lee, D.W. and Kim, Y.T. (l993):** effect of subchronic administration of antioxidants against cigarette smoke exposure in rats. Arch.. Toxicol., 67 (10): 667-673.
50. **Shoji, S. (l974):** Some chemical studies on ginseng. I proceedings of international Ginseng symposium, pp. 69-76. The central research -Institute, office of Monopoly, Republic of Korea .
51. **Stroeve, E.A. and Makarova, V.G. (l988):** Study in peroxide oxidation of biological membrane lipids. Chapter (15) Quoted from laboratory manual in Biochemistry " English transition", pp. 251-255.
52. **Takaku, T.; Kameda, K.; Matsuura, V.; Sekiya, K. and Okuda, H. (l990):** Studies on insulin-like substances in Korean red ginseg. Planta Medica. 56: 27-30.
53. **Tohn, H. (l994):** Improved isolated heart contractility and mitochondrial oxidation after chronic treatment with Panax ginseng in rats. Am. J.Clin. Med. 22 (3-4) : 275-284.
54. **Torres, M.I.; Fernandez, M.; Gil, A. and Rios, A.(l997):** Effect of dietary nucleotides on degree of fibrosis and steatosis induced by oral intake of thioacetamide. Dig.-Dis-Sci. 42 (6): 1322-8.
55. **Voces, J.; Alvarez, A., Vila, L.; Ferrando, A.; Cabral de Oliveira, C. and Prieto, J.G. (l999):** Effects of administration of the standarized *Panax ginseng* extract G115 on hepatic antioxidant function after exhaustive exercise.Comparative Biochemistry and physiology. 123: 175-184.
56. **Whanger, P.D. (l992):** Selenium in the treatment of heavy metals poinsoning and chemical carcinogenesis. Trace-Element Electrolytes Health Dis., 6 (1): 209-2221 .
57. **Xiaoguang, C.; Hongyan, L.; Xiaohong, Z.; Zhaodi, F. ; Yan,L.; Lihua, T. and Rui, H. (l998):** Cancer chemoprevente and therapeutic activities of red ginseng. J. Ethopharmacol., 60 (1): 71-78.
58. **Yo Kozawa, T.; Yasui, T. and Qura, H. (l996):** Molecular biological analysis of the effects of ginenoside-Rb2 on albumin mRNA in streptozotocin induced diabetic rats. J. Pharmacol. (48): , 763-767.
59. **Yun, T.K.; Lee, Y.S.; Kwon, H.Y. and Choi, K.J. (1996):** Saponin contents and anticarcinogenic effects of ginseng depending on types and ages in mice. Chung. Kuo, Yao. Li Hsuch. Pao, 17, 4: 293-298.
60. **Yun, T.K. and Choi, S.U. (l998):** Non-organ specific cancer prevention of ginseng a preventive study in Korea. Int. J. Epidemoil , 27, 3: 359-364.
61. **Zhang, D.; Yasuda, T.; Yu, Y.; Zheng, P.; Kawabata,T.;Ma, Y. and Okadas, S. (l996) :** Ginseng extract scavenges hydroxyl radical and protects unsatutrated fatty acids from decomposition caused by iron-mediated lipid peroxidation. Free Rad. Biol. 20: 145-150.
62. **Zim mermann, T.; Franke, H. and Dargel, R. (l986):** Studies on lipid and lipoprotein metabolism in rat liver cirrhosis induced by different regimens of thioacetaminde administration. Exp. Pathol. 30, 109-117.
63. **Zimmermann, T.; Muller, A.; Machnik, G.; Franke, H.; Schubert, H. and Dargel, R. (l987):** Biochemical and morphological studies on production and regression of experimental liver cirrhosis induced by thioacetamide in Jue: WIS rats Z. Versuchstierkol 30, 165. 180.
64. **Zuin, M. ; Battezzati, P.M.; Camisasca, M.; Riebenefeld, D. and Podda, M. (l987):** Effects of a preparation containing a standardized ginseng extract combined with trace elements against hepatotoxin induced chronic liver disease in elderly. J. Int. Med. Res., 15: 276-281.

مقدرة الجينسج المضادة للتسمم الكبدي المحدث بالثيواسيتاميد فى الجرذان البيضاء

1- أميرة تهامى إبراهيم ، أحكام الجندي,2- بشرى الظواهرى.

1 – قسم علم الحيوان – كلية العلوم جامعة الأزهر للبنات ,2- قسم فسيولوجى- كلية طب جامعة الأزهر للبنات

يعتبر مركب النيوأسيتاميد من المركبات السامة والضارة جداً للصحة وخصوصا الإنسان . ولذلك فقد أدى إعطاء جرعة مقدارها 50 ميللجرام /كيلوجرام من وزن الجسم للجرذان إلى زيادة ملحوظة فى أنزيمات الكبد وأنسجته كلها وخاصة عند 48 و 72 ساعة من إعطاء الثيواسيتاميد وأيضا أدى إلى زيادة واضحة وملحوظة فى أنزيمات الكبد المضادة للأكسدة مثل أنز يم الجلوتاثيون ريداكتيز (GSSG-R) بينما ظل فى معدلة الطبيعى أنزيم الجلوتاثيون المختزل (GSH) بينما زادت نسبة الدهون الفوقية Lipid preoxidation فى أنسجة الكبد زيادة ملحوظة .

وقد سببت جذور نبات الجينسج انخفاضا لاثار النيواسيتاميد وكان لا عطاءه بجرعة مقدارها 117 ملليللجرام /كيلوجرام من وزن الجسم يوميا ولمدة 10 أيام قبل إعطاء النيواسيتاميد أثراً واقياً ضد هذه السمية .