Potential impact of *Panax ginseng* against ethanol induced hyperlipidemia and cardiac damage in rats

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Abstract: The objective of the current work was to explore the possible hypolipidemic and therapeutic impacts of *Panax ginseng* against cardiac damage in response to ethanol ingestion in male and female rats. 10% ethanol was ingested (2ml/Kg) to both male and female rats daily for fourteen days. The results showed that ingestion of *ginseng* (150mg/Kg) daily for six weeks to male and female rats intoxicated with ethanol, two weeks after ethanol ingestion, successfully modulated the alterations in the serum lipid profiles, namely, triglycerides (TGs), total cholesterol (TCh), low density lipoprotein (LDL-C) and high density lipoprotein (HDL-C), in male and female rats exposed to ethanol versus untreated intoxicated ones. The plant also pronouncedly attenuated the increases in serum cardiac damage biomarkers, namely lactate dehydrogenase (LDH) and creatine phosphokinase (CPK) compared with ethanol intoxicated untreated rats. In conclusion, this study showed that *Panax ginseng* has a beneficial impact against ethanol induced hyperlipidemia as a risk element for cardiovascular illness.

Keywords: *Panax ginseng*, ethanol, hyperlipidemia, cardiac damage.

INTRODUCTION

Excessive ethanol consumption is considered one of the potent reasons of death and morbidity worldwide. Ethanol abuse can induce many illness, such as cardiomyopathy, liver injury, cancers, neuro-degeneration (Donohue, 2007, Krenz and Korthuis, 2012; Sidharthan and Kottilil 2014; Goldowitz *et al*., 2014), bone disorder, Alzheimer's disease, and diabetes mellitus (Pietraszek *et al*., 2010; Ehrlich and Humpel , 2012). Hperlipidemia is one of the risk factors of ethanol induced cardiomyopathy. Ethanol is a potent stimulator of dyslipidemia in humans and rodents (Avogaro and Cazzolatu, 1975). Chronic alcohol feeding can cause a change in the lipid metabolism (Hirayama *et al.*, 1979, Weidman *et al.,* 1982).

Some authors have reported that chronic alcohol intake promotes a disorder in lipid metabolism of serum and tissue and produces dyslipidemia (Baraona and Lieber, 1979; Baraona *et al*., 1983; Remla *et al.,* 1991). An excessive lipid concentration in the circulation may alter the lipoprotein metabolism and lead to hypercholesterolemia, hypertriglyceridemia or both, the key factor in the development of cardiovascular diseases (Henry and Ginsberg, 2002). Some studies have revealed that the blood hyperlipidemia could relate to the atherosclerosis and the cardiovascular related diseases, the most common cause of morbidity and death (Diego *et al.,* 2006; Hicham *et al.,* 2008).

Reducing hyperlipidemia using natural products is an important strategy to suppress or mitigate atherosclerosis and decrease the cardiovascular events. Based on this criterion, a number of plants have been shown to reduce blood hyperlipidemia (Nicdao and Ai, 2014).

Panax ginseng C.A. Meyer (Araliaceae) is one of the major prevalent natural tonics with fleshy roots. It present in China, Japan, and Russia. The name Panax means "all cure," which describes the traditional conception that ginseng plant has the power to heal all the disorders of the body (Hofseth and Wargovich, 2007). It has been reported that ginseng has many medicinal characters, including protein anabolic effect, anticancer, and suppressing impact on cancer angiogenesis (Sato *et al.,* 1994). Also, ginseng has been utilized in alleviating cardiac failure and preserve tissues from oxidative injury (Wagner and Liu, 1987). *Panax ginseng's* has been reported to have a cardioprotective effect against ischemia re-oxygenation damage (Pei *et al.,* 2013). The major active compounds are polysaccharides, phenolic compounds, ginsenosides, amino acids, polyacetylenes and alkaloids (Attele *et al.,* 1999). Ginsenosides (glycosides) contain an aglycone (protopanaxatriol), is the most active component of ginseng and have been shown to possess a wide range of therapeutic impacts, such as immunomodulatory, antioxidant, anti-inflammatory, and anticancer activities (Attele *et al.,* 1999; Kenarova *et al.,* 1990; Park *et al*., 2003; Shibata, 2001). Extracts rich in phenolic compounds from this plant has been reported to posses hypolipidemic and antioxidant impacts (Lee *et al.,* 2013).

The objective of this work was to assess the hypolipidemic and medicinal impacts of *Panax ginseng* to antagonize hyperlipidemic cardiac damage induced in male and female rats in response to exposure to ethanol toxicity.

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MATERIALS AND METHODS

Chemicals

The utilized chemical reagents were pure, obtained from Sigma and Merck companies. Kits utilized for the estimation of different markers were bought from Biogamma, Stanbio, West Germany.

Plant

American *Panax ginseng* is 100% pure herbal root extract complex from red and white *ginseng*. The extract made in USA. The product was obtained from General Nutrition Centers (GNC) as supplement.

Animals and experimental design

Thirty adult male and thirty adult female albino Wister rats (190-200g) were utilized for the present experiment. The rats were gotten from Experimental Animal Center, King Abdulaziz University, Jeddah, Saudi Arabia. Animal utilization protocols were approved by the Animal Care and Committee of the King Abdulaziz University (Reference No 1005-15). The rats were kept in special enclosure at optimum state (20±3°C, humidity 60-70%, and 12-h light/12h dark cycle). The animals were fed standard rat chow and tap water *ad libitum*. One week after adaptation, the rats randomly were classified into six groups, three male groups and three female groups, each of ten rats

Group 1 & 2: normal male (group 1) and female (group 2) rats.
Group 3 & 4: male (group 3) and female (group 4) animals intoxicated with 10% ethanol
Group 5 & 6: male (group 5) and female (group 6) animals intoxicated with 10% ethanol and treated with ginseng daily for six weeks

Ethanol (10%) was ingested orally (2ml/Kg/day, equivalent to 1.58g of ethanol/kg (Dogan and Celik, 2012) for two weeks. Ginseng was orally administered (150mg/Kg body weight) daily for six weeks to male and female intoxicated rats, two weeks after ethanol ingestion. Eight weeks later, the animals were maintained fasting (12-14h) over night, the blood specimens were gathered from the rats into clean tubes for clotting and serum isolation. Serum was isolated by centrifugation at 4000 r.p.m. for 15 min. and utilized to assess the biochemical parameters.

Biochemical serum assays

Lipid profiles were determined in serum, including, total cholesterol (Stein 1986), HDL- C (Stein, 1986) and TGs (Wahelfed, 1974). LDL can be calculated as follows: LDL= total cholesterol-HDL-TG/5. Heart function biomarkers, including, LDH (Bergmeyer, 1975) and CPK (Meada *et al.*, 1991) were also estimated

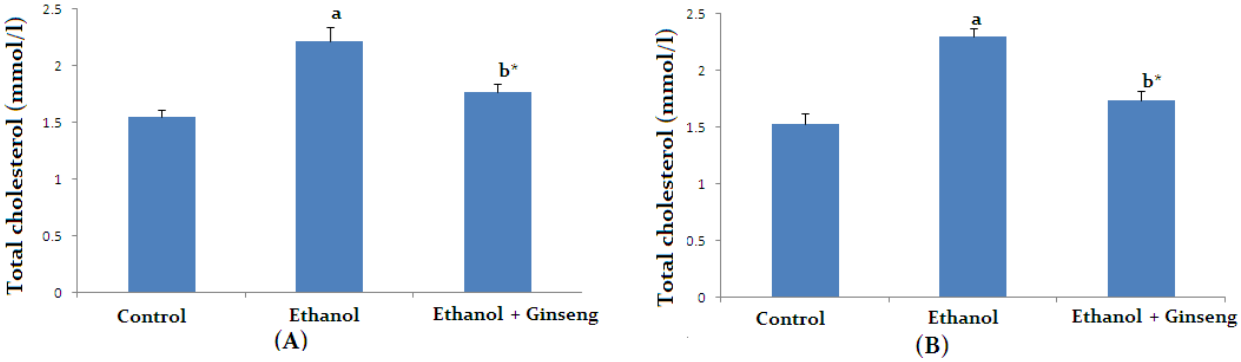

Fig. 1: Serum cholesterol level in male (A) and female (B) rats of control and ethanol treated groups. Results are denoted as mean ± SE of 6 rats, $^{a}P\leq0.001$, $^{b}P\leq0.05$ versus control, $^{*}P\leq0.001$ versus ethanol intoxicated group.

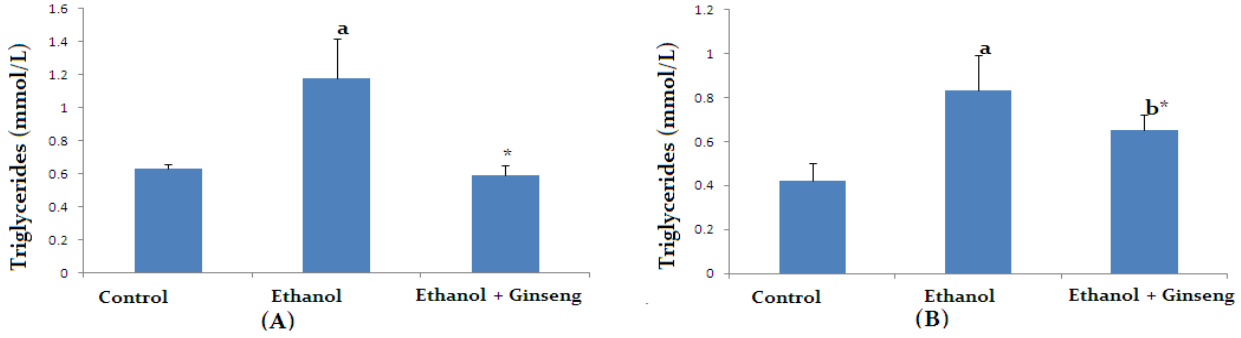

Fig. 2: Serum triglycerides level in male (A) and female (B) rats of control and ethanol treated groups. Data are denoted as mean ± SE of 6 rats, $^{a}P\leq0.001$, $^{b}P\leq0.01$ versus control, $^{*}P\leq0.001$ versus ethanol intoxicated group.

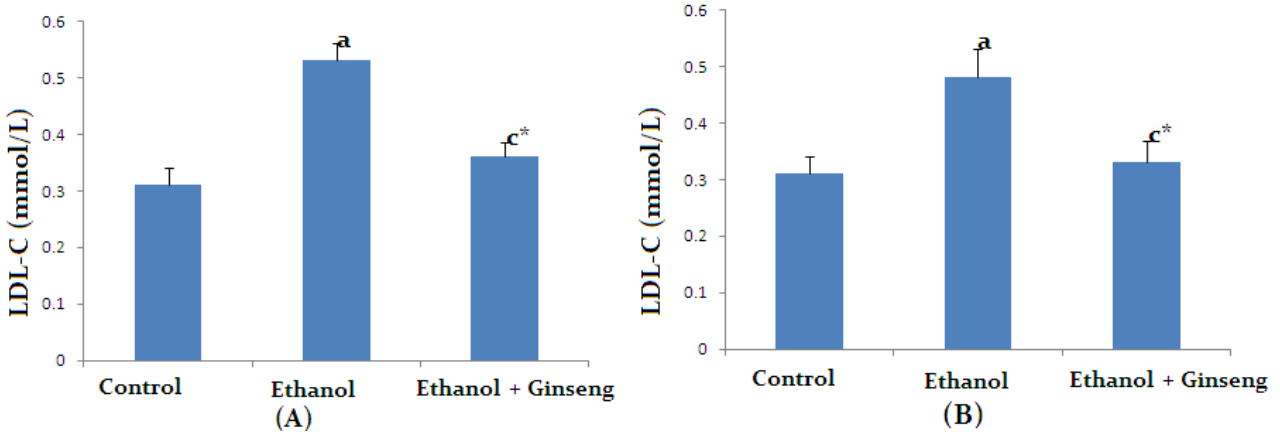

Fig. 3: Serum LDL-C level in male (A) and female (B) rats of control and ethanol treated groups. Results are denoted as mean ± SE of 6 rats, $^{a}P \leq 0.001$, $^{c}P \leq 0.05$ versus control, $^{*}P \leq 0.001$ versus ethanol intoxicated group.

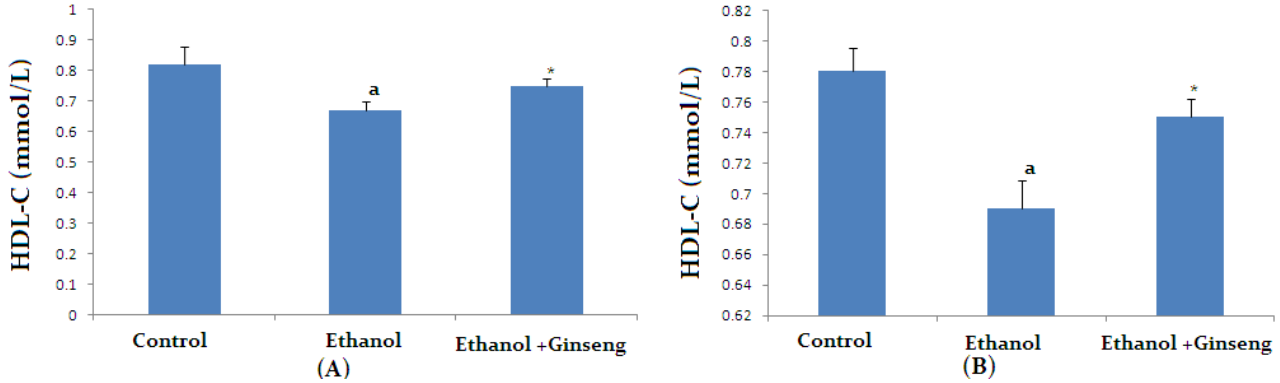

Fig. 4: Serum HDL-C level in male (A) and female (B) rats of control and ethanol treated groups. Results are denoted as mean ± SE of 6 rats, $^{a}P \leq 0.001$, versus control, $^{*}P \leq 0.001$ versus ethanol intoxicated group.

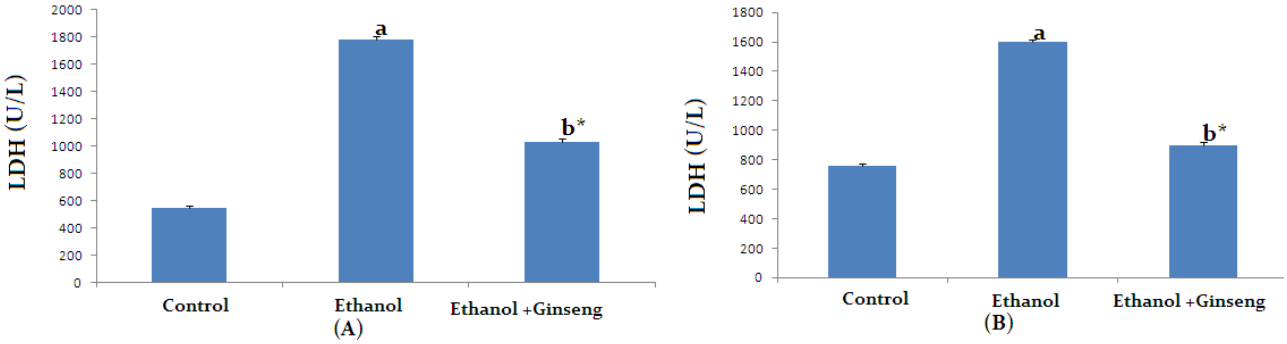

Fig. 5: Serum LDH activity in male (A) and female (B) rats of control and ethanol treated groups. Data are denoted as mean ± SE of 6 rats. $^{a}P \leq 0.001$, $^{b}P \leq 0.01$ versus control, $^{*}P \leq 0.001$ versus ethanol intoxicated group.

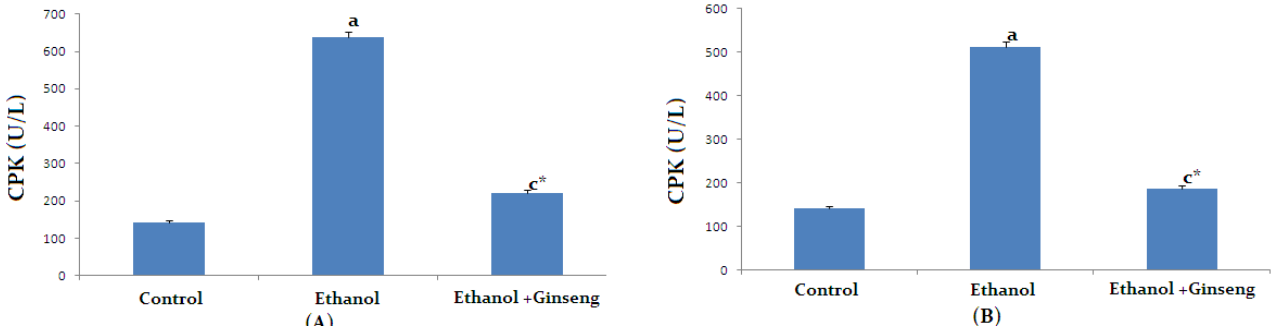

Fig. 6: Serum CPK activity in male (A) and female (B) rats of control and ethanol treated groups. Results are denoted as mean ± SE of 6 rats. $^{a}P \leq 0.001$, $^{c}P \leq 0.05$ versus control, $^{*}P \leq 0.001$ with ethanol intoxicated group.

STATISTICAL ANALYSIS

Analysis of data were performed by comparing the mean values of various groups with the mean values of control animals. Results were represented as mean ± S.E. The significant differences between groups were carried out by utilizing analysis of variance (one-way Anova) followed by Bonferroni as a post-ANOVA test.

RESULTS

Serum lipid concentrations of different experimental groups are shown in figs. 1-4. Marked increases in total cholesterol (fig. 1), TGs (fig. 2), LDL-C (fig. 3) with a concomitant decrease in HDL-C (fig. 4) were observed in ethanol intoxicated male and female rats with respect to control rats ($P \leq 0.001$). Intake of ginseng two weeks after ethanol intoxication, markedly ameliorated serum total hypercholesterolemia, hypertriglyceridemia, LDL-C and HDL-C versus ethanol intoxicated male and female counterpart rat group ($P \leq 0.001$).

Increases in the activities of serum LDH and CPK (figs. 5 & 6 respectively) as biomarkers of cardiac muscle damage, were recorded in male and female intoxicated rats versus control counterpart rat group ($P \leq 0.001$). Oral intake of ginseng to both rat sexes, two weeks after ethanol ingestion, effectively ameliorated the alteration in the above cardiac function biomarkers compared with intoxicated counterpart group ($P \leq 0.001$)

DISCUSSION

This investigation demonstrated that intake of ethanol to either male and female rats induced hyperlipidemia in both rat sexes as indicated by increases in serum total cholesterol, triglycerides, and LDL-C accompanied with a drop in HDL-C level versus counterpart control group.

The present observation correlates with some investigations have stated that ethanol consumption induced hyperlipidemia in the blood and tissues (Baraona *et al.,* 1983; Kumar *et al.,* 2002). There is an interaction between ethanol and lipid metabolism. Ethanol is the favored fuel for the liver and can displace lipids as an energy source. This suppresses hepatic fat catabolism, causing fat retention (Leiber and Schmid, 1961). The hepatic fat retention stimulates the release of lipoproteins into the circulation, resulting in hyperlipidemia (Kumar *et al.,* 2002). Also, it was reported that dyslipidemia may be caused by endoplasmic reticulum proliferation after ethanol ingestion accompanied by increases the enzyme activities of triglycerides and lipoproteins metabolism (Baraona *et al.,* 1975). Alcohol consumption could induce the formation of fatty acids and cholesterol and inhibit their catabolism, causing their accumulation in circulation (Joseph *et al.,* 1991; Bradbury and Berk, 2004). Also, previous study stated that the hypercholesterolemia induced by alcohol intake may ascribe to the increased -hydroxy-methylglutaryl CoA (HMG CoA) reductase activity, which is the rate limiting enzyme in cholesterol synthesis (Ashakumari and Vijayammal, 1993).

Furthermore, it has been reported that microsomal activation due to chronic alcohol intake accelerates ethanol oxidation and stimulates the biosynthesis of TGs (Savolainen *et al.,* 1984). The elevation in the level of LDL-C with a drop in HDL-C may reflect that ethanol caused alteration in lipoprotein metabolism. Hyperlipidemia in the blood serum is recognized as the leading cause for coronary artery disease. LDL-C is a potent risk element for atherosclerosis and cardiovascular ailments (Maxfield and Tabas, 2005; Paez and Gomez, 2009). Lipid profile and their oxidation, specifically LDL aggregate in the wall of arteries, causing their hardening, resulting in atherosclerotic lesions (Paez and Gomez, 2009). LDL has the major role in the atheroma production, while the HDL has the principle impact in suppressing atheroma formation (Maxfield and Tabas, 2005). The antiatherosclerotic impact of HDL is due to its capability to eliminate cholesterol from arterial wall, induce prostacyclin production and repress the synthesis of adhesion biomolecules, thus decreasing cardiovascular disorders (Nofer *et al.,* 2002; Pal, 2009).

Decreasing the levels of plasma lipid through natural product may be effective in lowering the risk of cardiovascular morbidity.

Intake of ginseng to male and female intoxicated rats, markedly ameliorated the serum lipid profiles in relation to their counterparts, indicating its hypolipidemic beneficial action. Previous authors reported that ginseng saponin could reduce the cholesterol level in the circulation by increasing cholesterol release through bile acid biosynthesis (Joo, 1980; Yamamoto and Kumagai, 1980).

There are many investigations declared that chronic ethanol ingestion cause heart tissue damage (Pushpakiran *et al.,* 2004; Saravanan and Pugalendi , 2006; Kalaz *et al.,* 2012). In line with these investigations, this work demonstrated that ethanol ingestion to both male and female rats caused increases in the serum biomarkers of myocardial tissue damage including CPK and LDH. The elevated levels of these biomarkers may be attributed to their release from cardiac muscles to the circulation in response to cardiac muscle damage caused by ethanol toxicity. The release of these enzymes to blood stream may due to the alteration in the plasma membrane integrity of cardiac muscle cells per-oxidized by free oxygen radicals produced during ethanol metabolism (Saravanan and Pugalendi, 2006). Oxidative stress, caused cardiac muscle injury under the effect of ethanol

consumption, may be the causative factor leading to myocardial infarction (cell death). It has been reported that oxygen radical generation due to acute and chronic ethanol intake, causes deleterious impact on cardiac tissue through induction of lipid peroxidation (Kalaz *et al.,* 2012). Beside, the generation of inflammatory cytokines such as tumor necrosis factor -alpha (TNF- α) and disruption of calcium homeostasis of cardiac muscle cells due to ethanol toxicity, leading to calcium leakage (Ren and Wold, 2008). Mitochondrial calcium accumulation stimulates cytochrome c release, causing activation of caspases, and thus apoptotic cell death (Ren and Wold, 2008).

Treatment of ethanol intoxicated male and female rats with ginseng, markedly modulated the increases in the biomarkers of serum cardiac tissue damage compared with intoxicated untreated counterparts. This result may indicate the potential action of the used ginseng in treating cardiac tissue damage induced by ethanol toxicity. The cardio-protective impact of phenolic compounds from ginseng was previously proved which may be related to their antioxidant activity (Lee *et al.,* 2013)

In conclusion, the current investigation revealed that treatment with ginseng has a beneficial impact against ethanol induced hyperlipidemia, as a risk element for cardiovascular disorders. Ginseng also successfully could mitigate cardiac tissue injury due to ethanol toxicity. These data may suggest the utilization of ginseng as a therapeutic agent to attenuate hyperlipidemic cardiac damage and dysfunction in response to chemical toxins.

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