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Protective effect of *Panax ginseng* against N-acetyl-p-aminophenol-induced hepatotoxicity in rats

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*Panax ginseng* (PG) has been commonly used as medicinal herb for the treatment of various diseases in Eastern Asia for thousands of years. This study was designed to investigate the protective effect of PG against paracetamol-(N-acetyl-p-aminophenol; APAP)-induced liver damage in rats. Thirty-two albino Wistar rats were divided into four groups: Group C (control); Group APAP (gavaged orally with APAP, 2 g/kg, single dose); Group PG 100 mg/kg + APAP or 200 mg/kg + APAP (these two groups were treated by gavaging with PG (100 or 200 mg/kg) for 30 days following a single dose of APAP). APAP treatment alone induced hepatotoxicity, evidenced by significant increases in malondialdehyde (MDA) level and serum activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and tumor necrosis factor-α (TNF-α). In addition, the level of GSH in the liver was significantly reduced, as were the activities of superoxide dismutase (SOD) and catalase (CAT). Liver histopathological examination showed that APAP administration induced centrilobular necrosis and infiltration of lymphocytes. However, these biochemical and histological changes were prevented by PG pretreatment. In conclusion, our results suggest that PG may be considered a protective medicinal herb against APAP-induced liver injury.

Key words: *Panax ginseng*, N-acetyl-p-aminophenol, liver, oxidative damage, rat.

INTRODUCTION

The liver is the largest internal organ in the human (and some animal’s) body. It plays a key role in over 200 functions and in many biological activities, such as metabolism, digestion, elimination, and detoxification of xenobiotics, environmental pollutants and chemo-therapeutic agents, etc. (Maheswari, 2008). Liver toxiciations are frequent problems mainly caused by hepatotoxicants, including carbon tetrachloride (CCl4), nitrosamines, heavy metals and polycyclic aromatic hydrocarbons, as well as some synthetic pharmaceuticals. There are many causes of acute hepatic failure (AHF) except paracetamol toxicity. The basic etiopathogenic agents of AHF were viral hepatitis (39%), unknown cause (30%), toxins or drugs (21%) and others (10%) in Spain (Tost, 2000). The hepatitis B virus

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is the first important virus infection worldwide, responsible for 70% of all cases of viral origin (Lee, 2008). Other viruses involved contain the herpes virus, varicella-zoster, cytomegalovirus, Epstein-Barr virus, etc (O’Grady, 2005). Anti-bacterial drugs, chemicals or toxins such as amanitin, azoxymethane, carbon tetrachloride, concanavalin A, galactosamine thioacetamide, and lipopolysaccharide are among the pharmaceuticals that most commonly prompt AHF (Bernaue et al., 1986; Fontana, 2008; Tunon et al., 2009).

Paracetamol (also known as acetaminophen, N-acetyl-p-aminophenol; APAP) is a very effective drug widely used as an analgesic and antipyretic agent for relieving mild and moderate pain, which is safe and easily tolerated in therapeutic doses (Proudfoot and Wright, 1970). However, when given in large single-dose ingestions, APAP can induce liver, kidney, and other organ damages in both humans and animals (Wallace, 2004). Meanwhile, the main mechanism of APAP toxicity in the liver is not fully understood. At therapeutic doses, APAP mainly undergoes glucuronidation and sulfation in the liver. On the other hand, at over dosages, APAP is metabolized by the cytochrome P450 (CYP450) oxidative system that is mainly localized in the liver endoplasmic reticulum, and generates N-acetyl-p-benzoquinone-imine (NAPQI). This metabolite depletes hepatic glutathione and then binds covalently to intracellular proteins, including mitochondrial proteins. This situation leads to the formation of reactive oxygen and nitrogen species, and initiates lipid peroxidation that eventually results in destruction, necrosis, or apoptosis of the liver cells (Hinson et al., 2004; James et al., 2003; Nelson, 1990).

N-Acetylcysteine (NAC) is the antidote for acetaminophen poisoning because of its ability to increase the available glutathione for conjugation with NAPQI (Tucker, 1998). On the other hand, in clinical and experimental studies, many compounds have been investigated for their ability to protect against paracetamol-induced hepatotoxicity, and those possessing some useful features such as antioxidant, anticytokine, and anti-inflammatory properties were of particular interest (Chun et al., 2009; Jaeschke et al., 2011; Srivastava et al., 2010). However, the need for new treatment protocols remains high.

Herbal medicine, also known as phyotherapy, has been used for thousands of years in the treatment or prevention of many disorders. *Panax ginseng* (PG) is one of the most popular phytotherapeutic agents of Asian and Chinese medicine for patients with liver disease (Chung et al., 2011; Duke, 1989). The hepatoprotective effects of PG on cirrhosis and ischemic injury have been shown in previous studies using animal models (Park et al., 2010). Generally, the pharmacological action of PG is attributed to active compounds including ginsenosides, polyacetylenes, sesquiterpenes, peptidoglycans, and polysaccharides. To date, previous studies have demonstrated the protective effects of PG on cancer, diabetes, inflammation, brain, kidney, liver, heart, etc (Ibrahim, 2009). However, to the best of our knowledge, there are no sufficient data on the hepatoprotective effect of PG in experimental APAP toxicity. Therefore, the present study was designed to identify the protective effect of PG against APAP-induced hepatotoxicity in rats.

**MATERIALS AND METHODS**

**Chemicals**

Detection kits for superoxide dismutase activity (SOD), catalase activity (CAT), malondialdehyde (MDA), and glutathione (GSH) were purchased from Cayman and Cell Biolabs (USA), while Mouse tumor necrosis factor-α (TNF-α) enzyme-linked immunosorbent assay (ELISA) kit was obtained from Invitrogen-KRC3011 (USA). The alanine aminotransferase (ALT) and aspartate aminotransferase (AST) reagents were purchased from USCN Life Science (China). The Korean Society of Ginseng (Seoul, Korea) kindly gifted *P. ginseng*. All other reagents and chemicals were of analytical grade and purchased from commercial suppliers. This study was performed in the Research Laboratory of Basic and Clinical Medical Sciences and Drug Development at Atatürk University, School of Medicine, Department of Pharmacology.\*  

**Experimental animals**

Thirty-two adult male albino Wistar rats (n=8 x 4) weighing about 220-250 g were used. They were given standard rat pellet feed and tap water *ad libitum*. The rats were housed in individual cages (360 x 200 x 190 mm³), each containing two or three animals from 15 days before the start of the experiment. All animals were housed in stainless steel cages under standard laboratory conditions (light period 07.00 a.m. to 8.00 p.m., 21 ± 2°C, and relative humidity 55%) throughout the experimental period. The animal care and experimental protocols were approved by the Experimental Animal Ethics Committee, Atatürk University, Erzurum, Turkey.

**Experimental design**

Rats were divided into four groups, each containing eight animals. The first group served as healthy controls (Group C-control). Groups APAP, APAP + PG 100 mg/kg, and APAP + PG 200 mg/kg were treated with distilled water, PG 100 mg/kg, or PG 200 mg/kg p.o, respectively, every day for 28 days. On the 28th day of the study, all groups were fasted for 24 h. At the end of 28 days, Groups APAP, APAP+PG 100 mg/kg and APAP+PG 200 mg/kg were treated with APAP 2 g/kg, p.o. (dissolved in distilled water) (Bruck et al., 1999). These groups received distilled water, PG 100 or PG 200 mg/kg, respectively, immediately after administration of APAP.

**Blood and tissue sampling**

On the 30th day, after 24 h of APAP administration, the rats were anaesthetized with a high dose of pentothal sodium (50 mg/kg). Blood samples were collected from the heart, after which animals were then sacrificed. Serum samples were separated by centrifuging at 4000 rpm for 10 min at 4°C within 1 h after collection, and were stored in a −86°C freezer before being used for biochemical analysis (including ALT, AST, total protein, and TNF-α). The liver was removed immediately after sacrifice and divided into separate portions for analysis of antioxidant enzymes (GSH, SOD, and CAT) and MDA or fixed in 10% neutralized formalin for histopathological studies.
Serum measurements of ALT, AST, TNF-α, and total protein

To assess hepatic function, ALT and AST from each sample were measured in duplicate with highly sensitive ELISA kits specifically designed for rats, according to the manufacturer’s instructions (USCN life science-E90207Ra and E91214Ra (China), respectively). From each sample, TNF-α was measured in duplicate with a highly sensitive ELISA kit (Invitrogen-KRC3011 (USA)) specifically designed for rats, according to the manufacturer’s instructions. The protein concentrations were determined by the Lowry method using commercial protein standards (Sigma Aldrich, Total protein kit-TP0300-1KT-(USA)).

Biochemical investigation of liver tissues

After macroscopic analyses, rat tissues were kept at -86°C. Briefly, 100 mg of tissues from each rat was first perfused with phosphate buffered saline (PBS)/heparin and then homogenized in specific homogenate tampon (appropriate buffer) on ice by Ultra-Turrax homogenizer after grinding in liquid nitrogen. Then they were centrifuged according to manufacturer’s instructions. For biochemical investigation, SOD and CAT activity, and MDA and GSH levels from each supernatant were measured in duplicate with highly sensitive ELISA kits (Cayman-706002 and -707002 (USA), and Cell Biolabs-STA-330,312 (USA), respectively), specifically designed for rat tissue according to the manufacturer’s instructions. All the data were presented as the mean ± standard deviation (SD) results based on per mg of protein.

Histopathological examination

Small liver specimens were extracted, fixed in 10% buffered formalin, and processed routinely by embedding in paraffin. The paraffin blocks were cut 5-7 μM thick and stained with haematoxylin-eosin. The histopathological changes were evaluated under light microscope (BX41TF, Olympus Microsystems Corp., Japan) independently by a histologist blinded to the experiment.

Statistical analysis

The results were expressed as mean ± standard deviation (SD) of ten animals in each group. The data were subjected to one-way analysis of variance (ANOVA) followed by Tukey’s multiple comparison tests. Statistical significance was accepted for all tests at p<0.05.

RESULTS

Effects of PG on biochemical parameters in APAP-treated rats

No death was observed among animals in the control and other PG and APAP treated groups. The effects of PG and APAP on serum biochemical parameters are presented in Figure 1. According to the control group, APAP-induced liver injury was distinguishable by significantly increased liver ALT (Figure 1A) and AST (Figure 1B) levels (38.36 ± 10.98 versus 187.00 ± 26.16; 87.53 ± 11.28 versus 231.08 ± 33.58, respectively) (p<0.001). This result suggests that liver function markers are elevated in the serum due to release of the enzymes from damaged liver. Conversely, PG 100 mg/kg and PG 200 mg/kg pretreatment (plus APAP treatments) caused significantly decreased serum levels of ALT (Figure 1A) and AST (Figure 1B) (187.00 ± 26.16 versus 61.25 ± 23.73, and 52.75 ± 19.19 and 231.08 ± 33.58 versus 114.10±14.67 and 105.19±19.99, respectively) in a dose-dependent manner when compared with the APAP-only treated group (p<0.001). In addition, TNF-α levels were increased in the APAP treated groups compared with the control group (40.60 ± 5.45 versus 165.97 ± 28.50, p<0.001). In the PG 100 mg/kg + APAP and PG 200 mg/kg + APAP groups, TNF-α levels were reduced significantly (165.97 ± 28.50 versus 53.23 ± 6.85 and 49.09 ± 9.33, respectively, p<0.001) in a dose-dependent manner compared to the APAP-only group Figure 1C. Treatment of PG for 30 days prior to APAP administration provided significant protection to the liver, preventing the elevations of these enzymes and TNF-α level.

Effects of PG on MDA, GSH, SOD, and CAT in APAP-treated rats

The levels of MDA and GSH and activities of SOD and CAT enzymes for livers of all groups are presented in Figure 2. The liver MDA level was increased in the APAP group, while GSH level was decreased compared with the control group (1.67 ± 0.49 versus 4.70 ± 1.34, and 4.32 ± 1.81 versus 1.42 ± 0.34, respectively) (p<0.001). There were decreases in MDA level, but increases in GSH level in the PG 100 mg/kg pretreatment plus APAP. A decrease was also observed in PG 200 mg/kg pretreatment plus APAP groups compared with the APAP-only treated group in a dose-dependent manner (4.70 ± 1.34 versus 3.25 ± 0.370 (p<0.01), and 2.29 ± 0.84 (p<0.001) and 1.42 ± 0.34 versus 3.83 ± 1.37 (p<0.01) and 4.25 ± 1.01 (p<0.001), respectively) (Figure 2A and B).

In addition, APAP induced a noticeable decrease in the activities of liver SOD and CAT enzymes (21.31 ± 1.50 versus 14.12 ± 2.78 and 44.16 ± 5.47 versus 28.55 ± 6.16, respectively) (p<0.001). The other hand, PG 100 mg/kg and PG 200 mg/kg pretreatment caused significantly increased activities of SOD and CAT enzyme in a dose-dependent manner (14.12 ± 2.78 versus 18.56 ± 0.67 (p<0.01) and 20.43 ± 1.34 (p<0.001), respectively, and 28.55 ± 6.16 versus 42.26 ± 2.48 and 45.45 ± 4.03 (p<0.001), respectively), when compared with the APAP-only treated group (Figure 2C and D).

Effects of PG on histopathological changes of liver in APAP-treated rats

A histopathological assessment of the liver was performed for all groups. When the liver sections of the control groups were evaluated, the portal area consisted of bile duct and vascular structures as shown in the
normal histologic structure (Figure 3A). Additionally, hepatocytes close to this area had regular cell membrane and nucleus, and they were separated by sinusoids from each other (Figure 3A). In addition, the central vein in the middle of the hepatic lobule and hepatocytes, lined up radially from the vein, were seen as their natural structure (Figure 3B). Many necrotic foci were conspicuous at first glance in this APAP-only treated group (Figure 4A and B). Foci were found close to the central vein. In addition, many necrotic hepatocytes were detected around the central vein (Figure 4B).

On the other hand, in the PG 100 mg/kg + APAP group liver sections, all hepatocytes had eosinophilic cytoplasm, and sinusoids were narrowed and irregular shaped. In addition, the central and portal veins were filled with erythrocytes (Figure 5A and B). In contrast, in both in portal areas and central areas, many hepatocytes had normal appearance in the PG 200 mg/kg + APAP group’s liver sections (Figure 6A and B). However, a few hepatocytes with eosinophilic cytoplasm and hyperchromatic nuclei were observed. In addition, there were some inflammatory cells in sinusoids (Figure 6B).

**DISCUSSION**

APAP is the most common prescription for antipyretic and analgesic agents. It is safe in therapeutic doses, but can induce hepatic damage in high doses in laboratory animals and humans. APAP is metabolized and
saturated in the liver by sulfation and glucuronidation reactions, and then excreted by the kidney. At high dosage, APAP is oxidized to a highly reactive toxic metabolite (N-acetyl-p-benzoquinone imine (NAPQI)) by cytochrome enzymes, which is responsible for the liver damage (Demirbas et al., 2011; Naziroglu et al., 2009; Nelson, 1990). Reactive oxygen species (ROS) are generated under normal cellular conditions and are directly detoxified by antioxidant enzymes. Normally, there is a balance between cellular oxidant and antioxidant activity. However, excessive ROS production by NAPQI induces an imbalance of oxidative–antioxidative processes and leads to lipid peroxidation and antioxidant depletion, and increased release of proinflammatory cytokines. Thus, oxidative damage is an important mechanism in the development of APAP toxicity (Kanbur et al., 2009; McGill et al., 2012; Naziroglu et al., 2009). Medicinal plants have various effects on living organism, and they have been used for thousands years by humans. The in vivo previous studies reported that plant-derived phytotherapeutic agents (such as, curcumin, ellagic acid, resveratrol, and glycyrrhizin) have a significant contribution to the treatment of APAP-induced hepatic injury (Dhiman et al., 2012; Girish et al., 2009; Sener et al., 2006).

NAPQI can make covalent bound with cellular proteins, can change the structure and functions of these proteins. This cellular damages causes a decrease in calcium

**Figure 2.** Effect of treatment with PG or saline on liver GSH (A), MDA (B), SOD (C) and CAT (D) activity in APAP-induced rats. Results are means ± SD (n = 8). *Indicates p < 0.05; **indicates p < 0.01; ***indicates p <0.001.
ATPase activity and an increase in cytosolic calcium levels. As a result, cell permeability changes and lead to the lose of cellular integrity (Jaeschke et al., 2003; Jaeschke and Bajt, 2006). In addition, it has been shown that NAPQI can inhibit NADH and succinate dehydrogenase function (Burcham and Harman, 1991). It was considered that destruction of homeostasis was also responsible for high dose paracetamol induced hepatotoxicity (Boobis et al., 1990). As a result of destruction of homeostasis, intracellular Ca$^{2+}$ accumulates and an increase is shown in catabolic enzymes which causes cell death. Nitric oxide, reactive oxygens, lipid peroxidation and apoptosis are the major situations which play roles in hepatotoxicity (Donnelly et al., 1994; Nelson, 1990). In addition, peroxinitrite derivatives and protein nitrates also have roles in this condition (Gujral et al., 2002).

The determination of enzyme levels such as AST and ALT are commonly used as hepatic marker in assessment of APAP-induced liver damage (Yanpallewar et al., 2003; Yen et al., 2008). AST is mainly found in mitochondria of hepatocytes and cytoplasm of the liver, heart, skeletal muscles, and red blood cells. However, the ALT enzyme is found predominately in the hepatocyte cytoplasm and more specific to liver injury such as hepatitis, cirrhosis, or hepatic tumors. However, it is found in lesser quantities in other tissues such as the kidneys, heart, and skeletal muscle (Huang et al., 2008; Kuvandik et al., 2008). In the present study, findings showed that APAP treatment in rats cause significant increased the levels of AST and ALT. On the other hand, the pretreatment with PG significantly reduced the values of both enzymes as compared to the APAP-only treated group. These results are in agreement with the previous studies performed using PG and some hepatotoxic agents such as aflatoxin, carbon tetrachloride, and cadmium (Abdel-Wahhab et al., 2010; Cayir et al., 2011; Karakus et al., 2011). Hepatoprotective plants contain a variety of chemical components such as alkaloids, xanthenes, phenols, flavonoids, glycosides saponins, and terpenes (Bhawna, 2009). Previous studies have demonstrated that ginseng has antioxidant activity as it

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**Figure 3.** Control group’s liver section. A. Portal region of liver. Pa: portal area consisting of bile duct, portal vein, hepatic arteriole brunch. B. Central region of liver. CV: central vein. Section thickness, 5 µM; dye: H&E; bars 50 µM.

**Figure 4.** APAP-only treated group’s liver section. A. Portal region of liver; Pa: portal area; white arrow: necrotic focus; black arrow: apoptotic hepatocytes; CV: central vein. B: Central region of liver. Section thickness, 5 µM; dye: H&E.
contains ginsenosides, phenolic acids, flavonoids, and saponins. These properties of the ginseng are thought to provide many beneficial preventative effects against organ damage (He et al., 2012; Karakus et al., 2011; Ramesh et al., 2012). These findings could be interpreted as indicating that PG may possess the capacity to protect the structural integrity of hepatocytes and mitochondria from the damage induced by APAP.

Generation of ROS during the metabolism of APAP can cause abstraction of a hydrogen atom from an unsaturated lipid, initiating lipid peroxidation and finally, liver damage. Peroxidation of lipids causes severe impairments of the membrane structure and functions, DNA damage, cytotoxicity, and eventually cell death. MDA is one of the main lipid peroxidation products; it is a good marker of the degree of lipid peroxidation injury in hepatocytes (Bessems and Vermeulen, 2001; Fouad and Jresat, 2012). In the present study, MDA concentrations were greatly increased in liver tissue homogenates of rats treated with APAP in comparison with the control group. This situation is closely related to APAP-induced lipid peroxidation and damage to plasma membrane because of oxidative stress. However, pretreatment with PG significantly inhibited MDA level. This effect might be due to the potential antioxidant and free radical scavenging activities of PG. Also, these antioxidant and radical scavenging activities, and other effects such as antidiabetogenic, antiapoptotic, and immunomodulator activities of PG in pancreas, heart, liver, kidney, and blood tissues, have been demonstrated (Amin et al., 2011; Chen et al., 2011; Karakus et al., 2011; Liu et al., 2010).

Generally, antioxidant defense systems in mammalian tissues can be divided in two categories: enzymatic and non-enzymatic systems. GSH is a tripeptide nonenzymatic antioxidant that plays a central role in the
antioxidant defense system of the liver. It neutralizes ROS, such as hydrogen peroxide and superoxide radicals, by scavenging and antioxidant properties (Firuzi et al., 2011). The depletion of GSH storages in liver cells is known to play an important role in the paracetamol-overdose-induced hepatotoxicity. After depletion of liver GSH pool, NAPQI reacts with cellular lipids, proteins, and other cell structures, and subsequently leads to liver damage (Bessems and Vermeulen, 2001; McGill et al., 2012). In the present study, the GSH content in the APAP-treated group was substantially decreased. The groups pretreated with PG 100 mg/kg and PG 200 mg/kg exhibited significant increases in GSH content.

The super oxide dismutase (SOD) and catalase (CAT) enzymes are the members of the enzymatic antioxidant defense systems that protect the cell against oxidative damage induced by superoxide and hydrogen peroxide radicals. SOD enzyme converts superoxide radicals into molecular oxygen and hydrogen peroxide, while CAT converts hydrogen peroxide into water and oxygen (Firuzi et al., 2011; Weydert and Cullen, 2010). In the present study, the liver of both SOD and CAT enzyme activities were significantly lower in the APAP-only treated group. The cause of these reductions can be as a result of futile cycling of P450 caused by NAPQI, which consumed NADPH associated with reduction of molecular superoxide radical. However, the liver SOD and CAT enzyme activities in both doses of the PG pretreated groups were significantly increased compared with the APAP-only treated group. This hepatoprotective, antioxidant, and free radical scavenger activities of PG are attributed to its active compounds via regulatory effects on cellular permeability, stability, and suppressing cellular oxidative stress (Lu et al., 2009; Ramesh et al., 2012). Also, Kim et al. (1996) and Chang et al. (1999) reported that PG enhances gene transcription related to SOD and CAT enzymes (Chang et al., 1999; Kim et al., 1996). Also, the present authors recently demonstrated that PG protects the liver against free radical injury induced by CCl4 in rat (Karakuş et al., 2011). It was also demonstrated that PG protects liver from oxidative damage induced by cadmium (Shukla and Kumar, 2009).

TNF-α is one of the most important proinflammatory cytokines that mediates the acute-phase responses of various hepatotoxictants such as CCl4, cadmium, and APAP (Bradham et al., 1998). Recent studies have been reported that APAP-induced hepatotoxicity is not only primarily initiated by NAPQI occurrence but also a contribution of the cytokine over production by inflammatory cells (Nelson, 1990). In the present study, the TNF-α level was markedly increased in the APAP-treated group. This result agrees with in vitro and in vivo studies by Masubuchi et al. (2003) and Matsumaru et al. (2003) who reported that TNF-α has an important role for expression of hepatotoxicity by APAP. However, the TNF-α level in both doses of the PG pretreated groups significantly decreased compared with the APAP-treated group. These biochemical results also supported the histopathological results from the livers, which revealed hepatocellular degeneration and inflammatory cell infiltration in the portal area. The liver of the control groups showed normal histological features. However, rats treated with APAP alone had damage to the hepatic cells. Conversely, PG pretreatment exhibited significantly less damage to the hepatic cells. Similar findings were also informed by Sener et al. (2006), Girish et al. (2009) and Fouad and Jresat (2012) and Fouad and Jresat (2012), who indicated the structural changes in the liver tissues of APAP-only treated animals, which is reversed by some phytotherapeutic agents.

Conclusion

Our results suggest that PG effectively protected against the APAP-overdose-induced liver damage in rats. The primary hepatoprotective effect afforded by PG can be attributed to its antioxidant properties by alleviation of GSH, SOD and CAT depletion, and inhibition of lipid peroxidation, and anti-inflammatory activities via inhibition of TNF-α. Therefore, PG might be used as a natural ingredient for the prevention of liver damage induced by APAP.

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