# Effect of *Panax notoginseng* on Hepatic Microvascular Dysfunction in Rats

Soo Kyoung Lee, Jun Gi Kim[1], Dall Young Choi[1], Won Hwan Park*

*Cardiovascular Medical Research Center and Department of Diagnostics,*
*1:Department of Pathology, College of Oriental Medicine, Dongguk University*

*Panax notoginseng* (Buck) F.H. Chen. root (PNS) is used as a therapeutic agent to stop haemorrhages and a tonic to promote health in Korean and Chinese medicine. The pharmacokinetic profiles of the main PNS are still not accurately investigated. Our preliminary aim is to elucidate the pharmacokinetics features of the PNS in rats. Objective of this study is to determine whether PNS affects hepatic microvascular dysfunction elicited by gut ischemia and reperfusion (I/R), since gut I/R causes hepatic microvascular dysfunction, and to investigate the role of nitric oxide (NO). NO has been found to be a modulator of the adhesive interactions between platelets and endothelial cells. Male Wistar rats were exposed to 30 min of gut ischemia followed by 60 min of reperfusion. Intravital microscopy was used to monitor the number of non-perfused sinusoids (NPS). In another set of experiments, PNS (1 g/kg per day intragastrically) was administered to rats for 7 days. In some experiments, dexamethasone (ST) (2 ㎎/㎏ per day intravenously) was administered. In control rats, gut I/R elicited increases in the number of NPS, and plasma TNF-α and ALT activities, and these changes were mitigated by the pretreatment with PNS. Pretreatment with an NO synthase inhibitor diminished the protective effects of PNS on the increase in NPS and plasma TNF-α levels, but not its effect on the increase in plasma ALT activities. Pretreatment with PNS increased plasma nitrite/nitrate levels. The responses caused by gut I/R were attenuated by the pretreatment with ST. Pretreatment with an NO synthase inhibitor did not affect the effect of ST. These results suggest that PNS attenuates the gut I/R-induced hepatic microvascular dysfunction and inflammatory responses such as TNF-α production in the early phase via enhancement of NO production, and sequential hepatocellular damage via its anti-inflammatory effect like corticosteroid effect.

Key words : *Panax notoginseng*(PNS), Nitric oxide (NO), the microvascular dysfunction

## Introduction

Herbal medicines that have been used in Korea for thousands of years are now being manufactured as drugs containing ingredients of standardized quality and quantity. The clinical efficacy of these medicines has been used by Korean Western-medicine practitioners for more than 20 years and is well recognized[1]. One of the herbal medicines, Panax notoginseng, is the most common drug to treat chronic liver disease in Korea. A herbal medicine, *Panax notoginseng* (Buck) F.H. Chen. root (PNS) is highly prized in Korea for its therapeutic abilities to stop haemorrhages, to influence blood circulation and to act as a tonic agent. The main root of this plant, named notoginseng, is used for treatment of trauma and bleeding due to internal and external injury. *Panax notoginseng* has many reported actions such as limitation of liver injury, anti-tumor effect, and alteration of the functional balance of the immune system[2]. Recently, *P. notoginseng* is widely used by patients with chronic hepatitis in Korean. The preparation prevented liver fibrosis as well as the development of HCC in patients with cirrhosis[3]. In addition, *P. notoginseng* was found to inhibit the activation of stellate cells, the rodent equivalent of human stellate cells. This is believed to be the mechanism of prevention of liver fibrosis by PNS[3].

As the principal constituents of this medicinal herb, various dammarane-type triterpene saponins were isolated from the roots, leaves, and seeds[4]. Furthermore, its immunological adjuvant activities of the principal dammarane-type triterpene saponins from notoginseng and American ginseng were characterized[4]. Because of its major pharmaceutical effects, *P. notoginseng* is presumed to generally and gradually improve biological defense mechanisms, and it has been reported to have an anti-inflammatory action via an increase in blood corticosterone levels. However, its mode of

* To whom correspondence should be addressed at : Won Hwan Park, Cardiovascular Medical Research Center and Dept. of Diagnostics, Dongguk University, Sukjang-Dong 707, Kyung-Ju 780-714, Korea.
· E-mail : diapwh@dongguk.ac.kr, · Tel : 054-770-2373
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action has not been fully elucidated. It was also found that the saponin fraction from the flower buds of *P. notoginseng* showed hepatoprotective effect on liver injury induced by D-galactosamine (D-GalN) and lipopolysaccharide (LPS) in mice. The flower buds of *P. notoginseng* have been used for treatment of hypertension, vertigo, tinnitus, and laryngopharyngitis, and several known dammarane-type triterpene saponins were hitherto isolated from the flower buds[5]. New saponins from the flower buds of *P. notoginseng* as well as the hepatoprotective effects of the principal dammarane-type triterpene saponins have been characterized from the flower buds and roots[6,7].

Recent studies demonstrated various pharmacological effects of notoginsenosides: improving left ventricular diastolic function in hypertension patients, protecting the damage resulted from myocardial ischemia[2], inhibiting the increase of [$Ca^{2+}$] induced by KCl and glutamate or during hypoxemia[8,9]; blocking the $Ca^{2+}$ overload and $Ca^{2+}$-calmodulin complex production in nerve cell after cranial cerebral injury and thereby to protect the injured brain[10]; showing an obvious anti-inflammatory effect due to reduction the level of the intracellular free calcium concentration in neutrophils[11]; promoting the apoptosis of renal interstitial fibroblasts and taking effect to renal interstitial fibrosis[3]. PNS, in addition, can promote the synthesis of DNA and protein[12], modulate emotional responses in rats[13] and their metabolites show anticancer action[14]. Currently, PNS are used to treat coronary heart disease, cardiac angina, apoplexy and atherosclerosis in clinic. PNS contain several kinds of active components such as ginsenoside Rb1 and Rg1[15]. Rb1, one of the main 20 (S)-protopanaxadiol group saponins, shows effective anti-inflammatory action, obvious vasodilating effect and tranquillizing function to central nervous system. 20 (S)-protopanaxatrial group, represented by Rg1, possess the properties of exciting central nervous system, anti-fatigue and hemolysis[10]. It has not been reported about pharmacokinetics of the main saponins contained in PNS by more accurate method.

Nitric oxide (NO) has been found to be a modulator of the adhesive interactions between platelets and endothelial cells[16-18], as well as an important modulator of tissue blood flow, arterial pressure, and neurotransmission[18], and NO-dependent cell-cell interactions have been demonstrated in tissues exposed to ischemia and reperfusion (I/R), an injury process in which leucocyte-endothelial cell adhesion plays a critical role. A role of NO in the pathobiology of I/R injury has been supported by observations that inhibition of NO biosynthesis elicits most of the microvascular alterations observed in tissues exposed to I/R[17,19], and NO-donating compounds have shown to provide significant protection against the microvascular dysfunction that is normally associated with I/R[17]. Horie et al. developed a murine model of leucocyte-dependent hepatocellular dysfunction that is elicited by gut I/R.[17,20]. They have recently demonstrated that both inhibition of NO synthase and supplementation with exogenous NO affects the leucocyte rolling, leucocyte adhesion, and sinusoidal perfusion elicited in the liver by gut I/R[21].

Some herbal medicines have been reported to have an inducing effect on NO production by nonstimulated macrophages[22]. Sho-saiko-to has also been reported to stimulate NO production of cultured hepatocytes, and restore the NO production by macrophages reduced by oxidized low-density lipoprotein (Ox-LDL) and lysophosphatidylcholine[23]. However, little is known about the effect of the P. notoginseng-increased NO levels on I/R injury in vivo. In the present study, we investigated whether *P. notoginseng* modulates the gut I/R-induced microvascular dysfunction in the liver, and we investigated the role of NO in the responses by inhibiting NO synthase.

## Materials and methods

### 1. Plant Material

The roots of *Panax notoginseng* (Buck) F.H. Chen. root (PNS) were purchased in Kyungju, Kyungbuk Province, Korea. The roots of *Panax notoginseng* (Buck) F.H. Chen.(500 g) were finely cut and extracted three times by boiling water.

### 2. Animals and surgical procedure

For gut ischemia/reperfusion-induced hepatic microvascular dysfunction, male Wistar rats (200-250 g) were fed a standard rat chow for 2 weeks, and *P. notoginseng* (1 g/kg) in saline) or saline alone was then administered for 7 days intragastrically through a tube. The experiments below were performed 18 h after the final dose of *P. notoginseng* or saline was administered. The rats were fasted for 18 h prior to each experiment, and then intraperitoneally anesthetized with pentobarbital sodium (35 mg/kg). The left carotid artery was cannulated, and a catheter was positioned in the aortic arch to monitor blood pressure. The left jugular vein was cannulated for drug administration. All experiments were performed according to the criteria outlined in the Dongguk University Animal Care Guide.

### 3. Intravital microscopy

After laparotomy, one lobe of the liver was examined through an inverted intravital microscope (TMD-2S; Nikon,

Tokyo, Japan) and images were recorded with a silicon intensified target (SIT) camera (Hamamatsu photonicus, Shizuoka, Japan). The liver was placed on an adjustable Plexiglas microscope stage and covered with a non-fluorescent coverslip that allowed observation of a 2 ㎠ segment of tissue. The liver was carefully positioned to minimize the influence of respiratory movements, and its surface was moistened and covered with cotton gauze soaked with saline.

Images of microcirculation at the surface of the liver were observed through consecutive microfluorographs of hepatic microcirculation. The percentage of non-perfused sinusoids was calculated as the ratio of the number of non-perfused sinusoids to the total number of sinusiods per microscopic field.

4. Experimental protocols for gut ischemia/reperfusion-induced hepatic microvascular dysfunction in rats

We observed the surface of the liver for 10 min before ligating the superior mesenteric artery to ensure that all parameters measured on-line were in a steady state. The superior mesenteric artery was then ligated for 0 (sham) or 30 min with a snare created from polyethylene tubing. At the end of the ischemic period, the ligation was gently removed. The number of non-perfused sinusoids (NPS) were measured before ischemia, immediately following reperfusion, and every 15 min for 1 h thereafter. In one set of experiments, seven untreated animals, and five *P. notoginseng*-treated animals each in the control groups (sham gut I/R) and gut I/R groups were used. In another set of experiments in which *P. notoginseng* was administered, the rats were given a NO synthase (NOS) inhibitor, NG-monomethyl-L-arginine (L-NMMA; Sigma, St Louis, MO, USA) (0.5 ㎎/㎏), i.v. 30 min before the onset of ischemia. These experiments were performed with five animals in each group. In some experiments, the rats were given dexamethasone (2 ㎎/㎏; Sigma) with or without L-NMMA (0.5 ㎎/㎏), i.v. 30 min before the onset of ischemia. These experiments were performed with five animals in each group.

5. Tumor necrosis factor assay

At 60 min after the onset of reperfusion, blood plasma samples for tumor necrosis factor (TNF)-α levels were collected from the inferior vena cava at a point proximal to the hepatic vein. Plasma TNF-α concentration was determined in a microtiter plate using a TNF-α immunoassay kit (R&D, Camarillo, CA, USA) based on an enzyme-linked immunosorbent assay (ELISA).

6. Enzyme and nitrite/nitrate assay

Blood samples were collected from the carotid artery 6 h after the onset of reperfusion. Serum ALT activity was determined by using conventional UV methods as previously described[5]. Blood plasma samples were collected from the inferior vena cava 45 min after the administration of *P. notoginseng*(saline as control). The combined levels of nitrite and nitrate in plasma were determined by using a previously reported method[16]. Five separate experiments were performed.

7. Statistical analysis

For gut ischemia/reperfusion-induced hepatic microvascular dysfunction in rats, the data were analyzed by using standard statistical methods, that is, ANOVA and Scheffe's (post hoc) test. All values are reported as mean ± SEM. Statistical significance was considered to exist at $P< 0.05$.

# Results

1. Effects of *P. notoginseng* and/or a NOS inhibitor (L-NMMA) on the percentage of non-perfused sinusoids in rat liver at 60 min after gut ischemia (I)/reperfusion(R)

The effects of *P. notoginseng* and/or L-NMMA on the gut I/R-induced increase in percentage of non-perfused sinusoids (NPS). In control rats, gut I/R elicited (or induced) significant increases in NPS compared to basal values. Pretreatment with *P. notoginseng* blunted (or reduced) the gut ischemia/reperfusion-induced increases in non-perfused sinusoids (untreated + I/R: 19.3±1.3%, *P. notoginseng* + I/R: 12.8±0.5%). L-NMMA diminished the protective effects of *P. notoginseng* (NPS: 15.3±1.4%)(Fig. 1).

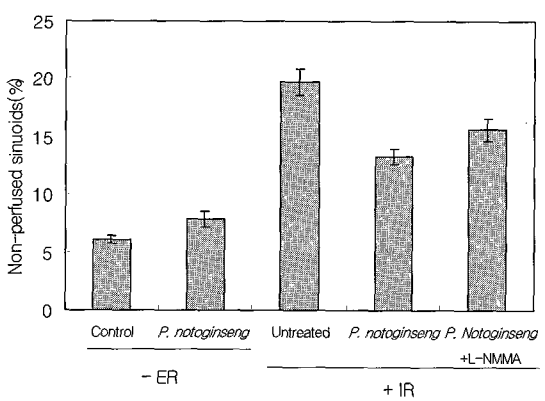


**Fig. 1. Effects of *P. notoginseng* and/or a NOS inhibitor (L-NMMA) on the percentage of non-perfused sinusoids in rat liver at 60 min after gut ischemia (I)/reperfusion(R).** The numbers of animals in each experimental group are controls = 6, I/R = 5, each group with P. notoginseng and/or L-NMMA = 5. *P< 0.05 versus control, # P< 0.05 versus untreated + I/R group.

2. Effects of *P. notoginseng*, dexamethasone and/or a NOS inhibitor (L-NMMA) on plasma tumor necrosis factor (TNF)-α levels in rat

liver at 60 min after gut ischemia (I)/reperfusion (R)

This illustrates the effect of *P. notoginseng* and/or L-NMMA on the gut I/R-induced elevation of plasma TNF-α levels. In the control rats, gut I/R elevated the plasma TNF-α levels. Pretreatment with *P. notoginseng*, however, blunted the gut I/R-induced elevation of plasma TNF-α levels (Untreated + I/R: 121.3±3.5, *P. notoginseng* + I/R: 61.4±6.7 pg/mℓ). L-NMMA diminished the protective effects of *P. notoginseng* (80.5±6.7 pg/mℓ). Pretreatment with dexamethasone also blunted the gut I/R-induced elevation of plasma TNF-α levels, but L-NMMA did not affect the protective effects of dexamethasone (ST) (ST + I/R: 48.4±8.2, ST + L-NMMA + I/R, 73.2±10.4 pg/mℓ)(Fig. 2).

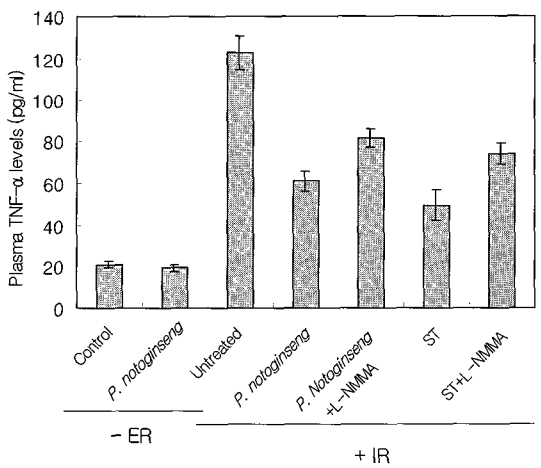


**Fig. 2. Effects of *P. notoginseng*, dexamethasone and/or a NOS inhibitor (L-NMMA) on plasma tumor necrosis factor (TNF)-α levels in rat liver at 60 min after gut ischemia (I)/reperfusion (R).** The numbers of animals in each experimental group are controls = 6, I/R = 6, each group with *P. notoginseng*, dexamethasone and/or L-NMMA = 5. *P< 0.05 versus control, P< 0.05 versus untreated + I/R group. ST, dexamethasone.

3. Effects of *P. notoginseng*, dexamethasone and/or a NOS inhibitor (L-NMMA) on plasma alanine aminotransferase (ALT) levels at 6 h after gut I/R

This illustrates the effect of *P. notoginseng* and/or L-NMMA on the gut I/R-induced elevation of plasma ALT activities. In the control rats, gut I/R elevated the plasma ALT activities. Pretreatment with *P. notoginseng*, however, blunted the gut I/R-induced elevation of plasma ALT levels (untreated + I/R: 128±15, *P. notoginseng* + I/R: 54.6±7.0 IU/L). L-NMMA did not affect the gut I/R-induced elevation of plasma ALT activities significantly (88±5.7 IU/ℓ). Pretreatment with dexamethasone also blunted the gut I/R-induced elevation of plasma ALT activities, and L-NMMA did not affect the protective effects of dexamethasone (ST) (ST + I/R: 49.4±5.1, ST + L-NMMA + I/R, 65.3±8.2 IU/ℓ)(Fig. 3).

4. Effects of *P. notoginseng* on plasma nitrite/nitrate levels.

This shows the effects of *P. notoginseng* on plasma nitrite/nitrate levels. Pretreatment with *P. notoginseng* increased the plasma nitrite/nitrate levels(Fig. 4).

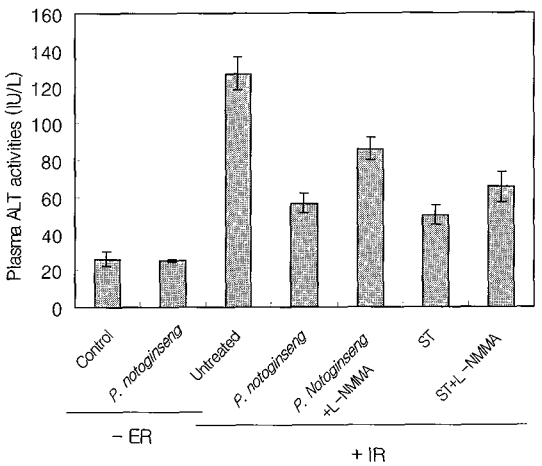


**Fig. 3. Effects of *P. notoginseng*, dexamethasone and/or a NOS inhibitor (L-NMMA) on plasma alanine aminotransferase (ALT) levels at 6 h after gut I/R.** The numbers of animals in each experimental group are five. *P< 0.05 versus control, P< 0.05 versus untreated + ischemia (I)/reperfusion (R) group. ST, dexamethasone.

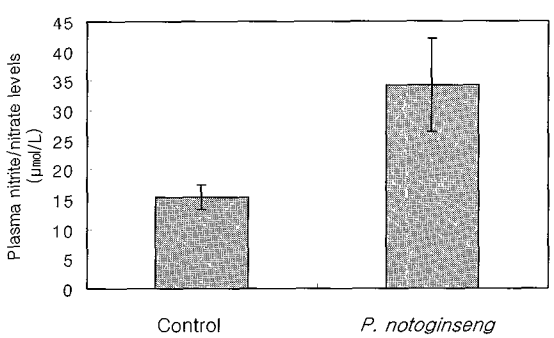


**Fig. 4. Effects of *P. notoginseng* on plasma nitrite/nitrate levels. *P. notoginseng* (1 g/kg per day) was administered to rats by a gastric tube for 7 days.** The numbers of animals in each experimental group are five. *P< 0.05 versus control.

## Discussion and Conclusion

The extract from the roots of *P. notoginseng* cultivated in Kyungbuk province of Korea was partitioned into a water to furnish a soluble fraction.

Previously, it was known that reperfusion of the ischemic small intestine elicits an acute inflammatory response both in the intestine and in distant organs, such as the liver[20,24] and lung[25]. In the liver, the response is characterized by leucocyte plugging of sinusoids, leucocyte adherence in postcapillary venules, a reduction in the number of perfused sinusoids, hepatocellular hypoxemia, and leakage of enzymes (ALT) from hepatocytes[20,25,26]. It was demonstrated that treatment with

L-NMMA results in cellular injury in the murine liver after gut I/R, and that increased delivery/generation of NO in the liver via an NO donor attenuates the inflammatory responses and microvascular dysfunction elicited in the liver by gut I/R[16,21]. These results suggest a protective effect of NO on the gut I/R-induced responses in the rat liver.

The finding in the present study that L-NMMA diminished the protective effect of *P. notoginseng* on the increase in plasma TNF-α levels in the pericentral region, and NPS suggests that *P. notoginseng* prevents the gut I/R-induced cytokine production and microvascular dysfunction in the liver by elevating the sinusoidal NO level. Several types of cell are known to produce NO, including endothelial cells[18], macrophages[18], neurons[27], and neutrophils[18], and the liver, for example, has the capacity to generate NO in three different resident cell populations, that is, Kupffer cells[28], hepatocytes and endothelial cells[18]. As NO has protective effects on I/R injury, the increase in NO production by hepatocytes and macrophages after treatment with *P. notoginseng* appears to be involved in the cytoprotective effects of *P. notoginseng*, and pretreatment with *P. notoginseng* actually increased plasma nitrite/nitrate levels in the present study. Our findings in the present study support our hypothesis that the *P. notoginseng* elevates NO levels, which in turn reduces or compensates the gut I/R-induced hepatic microcirculatory disturbance. As NO can modulate leucocyte- and/or platelet-endothelial cell interactions[17,18,21] the P. notoginseng-elevated NO levels in the liver appear to have an important role in in vivo hepatic inflammatory responses.

In the present study, however, L-NMMA did not affect the protective effect of *P. notoginseng* on the increase in the plasma ALT activity. One likely interpretation is that a mechanism other than the increase in NO production mediates the protective effects of *P. notoginseng*. In the present study, the gut I/R-induced cytokine production and microvascular dysfunction in the liver were attenuated by pretreatment with dexamethasone as well as *P. notoginseng*. Futhermore, L-NMMA did not affect either *P. notoginseng*- or a dexamethasone-induced decrease in the gut I/R-elevated plasma ALT activities. The findings in the present study support that *P. notoginseng* prevents the gut I/R-induced hepatocellular injury. However, the effect of *P. notoginseng* does not appear to play a role in its protective effect on the gut I/R-induced hepatic microvascular dysfunction in the early phase after reperfusion, because L-NMMA diminished the P. notoginseng-induced decrease in the gut I/R-elevated plasma TNF- levels but not the dexamethasone-induced decrease.

Another likely explanation of the absence of any significant effect of L-NMMA on the reduction of plasma ALT activity is that *P. notoginseng* has different effects on constitutive (endothelial) NOS (cNOS) and inducible NOS (iNOS). Although the isoform of NOS that contributes to these responses in the liver remains unclear, as several hours are required for the induction of inducible NOS[18], cNOS would seem to be involved in the early inflammatory responses observed in our in vivo model. In contrast, iNOS may be involved in the late inflammatory responses observed in our in vivo model. In this scenario, cNOS might be involved in the protective effects of *P. notoginseng* on the gut I/R-induced increase in leukostasis in the pericentral region and in NPS, and iNOS may be involved in the protective effects of *P. notoginseng* on the gut I/R-induced increase in plasma ALT activity. As the large amounts of NO induced by iNOS are known to have cytotoxic effects[29], *P. notoginseng* may prevent the gut I/R-induced increase in plasma ALT activity by reducing NO formation by iNOS. If *P. notoginseng* prevents the gut I/R-induced increase in plasma ALT activity by reducing NO formation by iNOS, it is not surprising that pretreatment with L-NMMA had no effect on the protective effect of *P. notoginseng*.

Although further studies are required to clarify the mechanisms of the protective effects of *P. notoginseng* on the reperfusion injury, the present study has demonstrated the protective effect of *P. notoginseng* on reperfusion injury via its corticosteroid effect, and the role of NO in the microvascular dysfunction in the early phase after reperfusion.

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