



PROTECTIVE EFFECTS OF KOREAN RED GINSENG EXTRACT
ON HEAVY METAL (ARSENIC)-INDUCED OXIDATIVE
STRESS, HYPERTENSION, AND BLOOD BIOCHEMICAL
CHANGES IN AN ANIMAL MODEL

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Summary

Kamruzzaman, S. M., M. Z. Uddin, M. Hasan, M. M. Islam, M. I. K. Ullah, M. R. Hossain & M. Rahman, 2025. Protective effects of Korean red ginseng extract on heavy metal (arsenic)-induced oxidative stress, hypertension, and blood biochemical changes in an animal model. *Bulg. J. Vet. Med.* (online first).

Korean red ginseng (KRG) is a traditional medicinal herb known to aid in stress adaptation, boost the immune system, enhance physical performance and provide several other health benefits. In contrast, arsenic (As) in its inorganic form is highly toxic and causes various physiological dysfunctions. The objective of this study was to investigate the effects of KRG extract on oxidative stress, blood pressure, and serum biochemical parameters in rats exposed to arsenic. Two hundred Sprague-Dawley rats were divided into four experimental groups and treated with 100 ppm sodium arsenite (NaAsO_2) in drinking water for 12 weeks, followed by administration of KRG extract at 100 mg/kg body weight /day for the same duration. Blood samples were collected to analyse plasma, serum, and haematological parameters. Exposure to arsenic resulted in increased blood pressure, white blood cell (WBC) count, alkaline phosphatase (ALP), aspartate and alanine transaminases (AST, ALT), serum creatinine, total protein, total bilirubin, triglyceride, high- and low-density lipoproteins (HDL, LDL), along with a significant reduction in red blood cell (RBC) count, plasma glutathione (GSH), catalase and superoxide dismutase activity. Treatment with KRG extract in arsenic-exposed rats significantly reduced systolic blood pressure, WBC count, ALP, AST, ALT, creatinine, total protein, total bilirubin, triglyceride, HDL, and LDL levels, increased plasma GSH, catalase and superoxide dismutase. No changes in heart rate or body weight were observed. These findings suggest that KRG extract mitigates oxidative stress and hypertension in arsenic-exposed rats, demonstrating its potential protective effects against arsenic-induced oxidative damage and high blood pressure.

Key words: arsenic, biochemical parameters, hypertension, Korean red ginseng extract, oxidative stress

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INTRODUCTION

Arsenic is widely dispersed throughout the atmosphere in the soil, air, and water as a naturally occurring component of the earth's crust. A minimum of 108 countries and about 230 million people have consumed drinking water containing arsenic at a level above the WHO provisional guideline value of 10 µg/L (UNICEF, 2018; Shaji *et al.*, 2021). Approximately 52 million people in Bangladesh have been exposed to arsenic through their drinking water (Yunus *et al.*, 2019; Bashir *et al.*, 2021). Chronical exposure to arsenic poses a high risk of adverse health effects like skin lesions and several chronic diseases such as cardiovascular diseases, hypertension, diabetes mellitus, chronic obstructive pulmonary diseases, cancers, etc. This often encourage policymakers to reconcentrate programmes for promoting child and adult survival (Saha & Ray, 2019; Rahaman *et al.*, 2021). Approximately 9,136 deaths and 174,174 disability-adjusted life years (undiscounted) lost occur per year in Bangladesh among the people exposed to >50 µg/L arsenic (Loewenberg, 2016).

Korean red ginseng, which is also referred to as *Panax ginseng*, has been utilized in traditional Korean medicine for millennia and offers a wide range of health advantages (Kim & Park, 2011; Park *et al.*, 2012; Yoon *et al.*, 2021). The adaptogenic properties of Korean ginseng, in adapting the body to stress and promoting balance are widely known. It is thought to strengthen the immune system, increase mental and physical stamina, and promote cognitive performance (Lee *et al.*, 2008; Endale *et al.*, 2012). Furthermore, Korean ginseng has antioxidant and anti-inflammatory properties that prolong life and protect against a number of ill-

nesses (Panwar *et al.*, 2005; Spelman *et al.*, 2006; Kang *et al.*, 2009).

Therefore, the aim of this research was to investigate the protective effects of Korean red ginseng extract on heavy metal (arsenic)-induced oxidative stress, hypertension, and changes in blood biochemical parameters in an animal model.

MATERIALS AND METHODS

Preparation and analysis of Korean red ginseng aqueous extract

The Korea Ginseng Corporation (Yuseong-gu, Daejeon, Korea) provided the red ginseng (KRG) aqueous extract. Using circulating hot water, the ginseng was steamed for three hours at 90–100 °C, dried at 50–80 °C, and extracted at 85–90 °C. The filtrate was lyophilised after being concentrated at a lower pressure. The active compounds of Korean red ginseng water extract are presented in Table 1.

Table 1. Detection and quantification of the active compounds from Korean red ginseng aqueous extract (KRG) by ultra-performance liquid chromatography from the Korea Ginseng Cooperation

Compound	KRG (mg/g)
Ginsenoside Rg1	0.69
Ginsenoside Re	0.82
Ginsenoside Rf	1.37
Ginsenoside Rg2f	1.50
Ginsenoside Rb1	5.85
Ginsenoside Rc	2.29
Ginsenoside Rb2	2.17
Ginsenoside Rd	0.89
Ginsenoside Rg3s	4.43
Ginsenoside Rg3r	2.02
Ginsenoside Rh1	1.28

Experiments on KRG extract were performed on a Waters ACQUITY ultra-performance liquid chromatography system (UPLC; Waters, Milford, MA, USA), including a binary solvent manager, sample manager, and a photodiode array detector (PDA). An Acquity UPLC BEH C18 column (2.1 mm × 50 mm, 1.7 µm; Waters 5) was used to perform the chromatographic separation of 2 µL of each sample injected to a gradient system at flow rate of 0.6 mL/min. Gradient elution was employed using solvent systems A (demonised water) and B (acetonitrile) at a temperature of 40 °C. The gradient programme used was as follows: initial 0–0.5 min, A/B (85:15, v/v); 0.5–14.5 min, linear change to A/B (70:30, v/v); 14.5–15.5 min, linear change to A/B (68:32, v/v); 15.5–16.5 min, linear change to A/B (60:40, v/v); 16.5–20 min, linear change to A/B (45:55, v/v); 20–23 min, linear change to A/B (10:90, v/v); 23–25 min, linear change to A/B (85:15, v/v) and was maintained for 2 min. As the chemical fingerprint analysis, chromatograms were measured using the detector wavelength (230 nm).

Experimental animals

All animal studies were approved by the Institutional Animal Care and Use Committee of Rajshahi University and performed in accordance with the guiding principles of animal research protocols. Two hundred (200) age-matched Sprague-Dawley (SD) rats with average weight 150 g and age 40 days were obtained from the International Centre for Diarrhoeal Disease Research, Bangladesh, Mohakhali (Dhaka, Bangladesh) and separated into four equal test groups: control, arsenic only (As), KRG only, and As with KRG (As+KRG). Each group of rats was housed in a 45×30 cm wire cage in 12/12-

hour light/dark cyclic conditions at a constant temperature of 25-30 °C at Narikelbari Farm, Rajshahi University, Bangladesh.

Arsenic exposure and Korean red ginseng treatment

Na-arsenite was purchased from Sigma-Aldrich (St. Louis, MO, USA). The control group received only *ad libitum* feed and drinking water for 12 weeks. The As group received *ad libitum* feed and drinking water containing arsenic at a concentration of 100 ppm for a period of 12 weeks. The KRG group received *ad libitum* feed and KRG extract administered orally through drinking water at a dose of 100 mg/kg/day for 12 weeks. Finally, the As+KRG group received *ad libitum* feed along with drinking water containing arsenic (100 ppm) and KRG extract (100 mg/kg/day) for the same duration.

Blood sampling and analysis

Briefly, an arterial blood sample was collected in an EDTA-coated tube and it was gently inverted several times to mix the anticoagulant. The sample was centrifuged (2000 × g, 5 mins) immediately to obtain plasma. Fasting blood samples were collected from the abdominal artery of a rat, and 5-7 ml of blood were left at room temperature for 30 minutes for clotting and subsequently centrifuged at 1,200 × g for 20 minutes. The supernatant was taken as serum and stored at -20 °C.

Plasma levels of glutathione were measured using the QuantiChrom Glutathione Assay Kit DIGT-250 (Gentaur, Brussels, Belgium). The activity of catalase was determined as described by Beers & Sizer (Beers & Sizer, 1952). The superoxide dismutase assay was done according to a method by Misra & Fridovich (Misra & Fridovich, 1972).

Serum liver enzyme activities were assayed on an analyzer (Robert Riele GmbH & Co KG, Berlin, Germany) and commercially available kits. Serum ALP activity was determined by a kit from Spinreact (Spain). AST, ALT, serum creatinine, and lipid profile parameters were measured by kits from Human (Germany). The mean values of all the samples were averaged from triplicate measurements.

Measurement of blood pressure

The body weights of all rats were recorded using a digital weighing scale. Systolic blood pressure was assessed non-invasively from the tail region at baseline and after 4, 8, and 12 weeks of treatment with a blood pressure monitoring device (Model ML125, AD Instruments, Colorado Springs, CO, USA). To minimise stress-induced variation, rats were gently restrained in holders and acclimatised by preheating in a chamber at 35 °C for approximately 15 min before measurement. A tail cuff equipped with a pneumatic pulse sensor was used for detection, and the final systolic pressure value for each rat was calculated as the mean of at least three consistent consecutive readings.

Statistical analysis

Data were analysed by SPSS software version 25.0 and expressed as mean ±

SEM (standard error of mean) values. The statistical significance among the experimental groups was assessed using repeated measures ANOVA and one-way ANOVA. Differences were considered statistically significant at $P < 0.01$ and $P < 0.05$.

RESULTS

Effect of KRG on arsenic-induced hypertension

An increase in blood pressure was observed at 8 weeks after exposure to arsenic alone (100 ppm), indicating that no significant change occurred during the initial 8 weeks of exposure. Following the course of therapy, rats treated with As+KRG showed a significant reduction in blood pressure ($P < 0.01$) compared with rats exposed to arsenic alone (150.4 ± 1.5 mmHg) and those treated with KRG only (116.2 ± 1.1 mmHg) (Table 2). This finding suggests that KRG effectively suppresses arsenic-induced hypertension.

Effect of KRG on arsenic-induced haematological alterations

The number of white blood cells in arsenic-exposed rats was significantly increased ($P < 0.05$) compared with controls, but no such difference was found when

Table 2. Effect of Korean red ginseng on body weight, systolic blood pressure and heart rate in control rats and rats treated with arsenic only (As); Korean red ginseng only (KRG) and both (As+KRG). Data are presented as mean ± SEM (n=10–12)

Parameters	Experimental groups			
	Control	As	KRG	As+KRG
Body weight (g)	215±4.3	220.0±5.2	208.0±4.4	210.0±5.8
Blood pressure (mmHg)	112±2.4	150.4±1.5	116.2±1.1	135.5±1.9*
Heart rate (beats per min)	410 ±5.3	406.0 ±4.9	415.0 ±5.2	408.0 ±6.1

* $P < 0.01$ vs the control group.

Table 3. Effect of Korean red ginseng on haematological alterations in control rats and rats treated with arsenic only (As); Korean red ginseng only (KRG) and both (As+KRG). Data are presented as mean \pm SEM, n=5

Haematological parameters	Experimental groups			
	Control	As	KRG	As+KRG
WBC ($10^9/L$)	6.50 \pm 0.15	8.50 \pm 0.45*	8.45 \pm 0.35*	7.20 \pm 0.42
RBC ($10^{12}/L$)	7.55 \pm 0.11	7.50 \pm 0.41*	7.10 \pm 0.43*	6.50 \pm 0.33
Hb (g/L)	156.0 \pm 2.20	155.0 \pm 2.50*	135.0 \pm 1.00*	122.0 \pm 2.40*
MCV (fL)	62.30 \pm 0.44	62.37 \pm 0.47	62.49 \pm 0.15	64.39 \pm 0.30
MCH (pg)	20.18 \pm 0.28	20.10 \pm 0.22	20.22 \pm 0.12	21.33 \pm 0.20
HCT (%)	46.04 \pm 0.39	47.07 \pm 0.30	45.36 \pm 0.37	42.32 \pm 0.32

* P<0.05 compared to the control group.

comparing controls with KRG-treated rats. The red blood cell counts in long-term arsenic-exposed rats was significantly (P<0.05) lower than that of untreated controls and KRG-treated rats. The red blood cell counts in As+KRG-treated rats were also lower than that of rats exposed to arsenic alone, but this difference was not statistically significant. Long-term KRG treatment increased the white blood cell counts, and this increase was significantly (P<0.05) different from controls. Arsenic plus KRG treatment reduced insignificantly the increased white blood cell counts compared with rats treated with arsenic alone. Haemoglobin (Hb) levels were significantly reduced, whereas mean corpuscular haemoglobin (MCH) showed a slight decrease in arsenic-treated rats. Hb levels did not recover following KRG treatment. Mean corpuscular volume (MCV) and haematocrit (HCT) were increased in arsenic-exposed rats, but MCV was not recovered by KRG therapy (Table 3).

Effect of KRG on kidney function and lipid profile blood parameters

The serum levels of AST, ALT, and ALP were measured to assess the hepatoprotec-

tive impact of KRG in rats treated with arsenic. The serum glucose and liver enzymes alkaline phosphatase (ALP), aspartate transaminase (AST), and alanine transaminase (ALT) were attenuated by KRG compared to normal. Two enzymes (AST and ALT) assessed were only significantly (P<0.05) increased in the As-exposed group. Serum creatinine, total protein, and total bilirubin levels also significantly (P<0.05) increased in the As-exposed rats compared to the untreated controls, KRG, or As+KRG-treated groups. Triglycerides, total, HDL, and LDL cholesterol levels in arsenic-treated rats were also increased (Table 4).

Effect of KRG on arsenic-induced oxidative injury

To evaluate the effect of chronic arsenic exposure on antioxidant capacity, plasma glutathione (GSH) levels were measured in rats. The mean GSH concentration in the control group was 61.9 \pm 7.9 μ M. Rats exposed to arsenic alone exhibited a significant decrease (P<0.01) in plasma GSH levels compared with controls. In contrast, rats treated with KRG alone or As+KRG maintained GSH concentrations that were

Table 4. Effect of Korean red ginseng on blood liver enzymes, creatinine, total protein, total bilirubin, and lipid profile parameters in control rats and rats treated with arsenic only (As); Korean red ginseng only (KRG) and both (As+KRG). Data are presented as mean \pm SEM, n=5

Parameters	Experimental groups			
	Control	As	KRG	As+KRG
Alkaline phosphatase (U/L)	145.81 \pm 3.60	199.50 \pm 5.30	140.40 \pm 2.50	160.10 \pm 2.67*
ALT (U/L)	69.40 \pm 2.15	95.20 \pm 3.50*	67.97 \pm 3.80	76.13 \pm 2.89
AST (IU/L)	60.50 \pm 2.20	85.65 \pm 1.35*	58.30 \pm 1.09	67.50 \pm 1.28*
Serum creatinine (μ mol/L)	25.00 \pm 0.13	35.00 \pm 0.13*	32.07 \pm 0.16*	30.40 \pm 0.18*
Total protein (g/L)	60.03 \pm 1.20	70.03 \pm 2.10*	65.24 \pm 0.19*	62.43 \pm 0.45
Total bilirubin (μ mol/L)	1.60 \pm 0.11	2.14 \pm 0.12*	2.00 \pm 0.13*	1.90 \pm 0.19*
Triglycerides (mmol/L)	0.75 \pm 0.19	0.95 \pm 0.05	0.88 \pm 0.04	0.80 \pm 0.08
Total cholesterol (mmol/L)	2.85 \pm 0.25	2.94 \pm 0.20	2.45 \pm 0.21	2.35 \pm 0.06
HDL cholesterol (mmol/L)	1.04 \pm 0.02	1.05 \pm 0.03	0.95 \pm 0.33	0.99 \pm 0.03
LDL cholesterol (mmol/L)	1.25 \pm 0.06	1.50 \pm 0.03	0.94 \pm 0.22	1.06 \pm 0.03

* P<0.05 compared to control group.

Table 5. Effect of Korean red ginseng on plasma glutathione concentrations, catalase and superoxide dismutase in control rats and rats treated either with arsenic only (As) or combined with Korean red ginseng (As+KRG). Data are presented as mean \pm SEM (n=5)

Parameters	Experimental groups		
	Control	As	As+KRG
Glutathione (μ M)	61.9 \pm 7.9	48.3 \pm 8.8*	59.4 \pm 7.8
Catalase activity (mMol/min)	8.1 \pm 1.0	4.8 \pm 1.0*	8.8 \pm 1.0
Superoxide dismutase activity (U/mg)	9980 \pm 900	5983.3 \pm 700*	8040.7 \pm 800

* P<0.01 vs the control group.

almost similar to those of the control group (Table 5).

The trends in catalase activity of rats that received As and Korean ginseng aqueous extract showed an insignificant change in the group that received 100 mg/kg of the extract (8.80 mMol/min) compared to the control group (8.10 mMol/min), whereas a significant decrease in catalase activity was observed in rats treated with arsenic alone (Table 5). Treatment with arsenic and 100 mg/kg KRG extract resulted in an insignificant change in SOD activity, with a value of 8040.7 U/mg protein, compared to the

control value of 9980 U/mg protein. However, a significant decrease in SOD activity was observed in rats that received arsenic only (5983.33 U/mg protein) compared to the control group (Table 5). In the present study, all antioxidant and antioxidant enzyme activities were significantly reduced in rats treated with As alone compared to the control. These activities, however, increased following co-administration of 100 mg/kg aqueous KRG extract.

DISCUSSION

This research on Korean ginseng was done to investigate its health benefits against arsenic exposure, as it is a global threat to healthy well-being. In this research, high blood pressure was observed in rats after exposure to arsenic in drinking water. Reduced systolic (mmHg) and diastolic (mmHg) blood pressure was observed when treated by KRG for a fixed period of time. A previous study showed that following a 12-week course of therapy (100 mg/kg/day), rats exposed to Pb plus KRG had blood pressure of 134.8 ± 2.0 mmHg, which was considerably lower than rats exposed to Pb alone (144.4 ± 1.5 mmHg) (Park *et al.*, 2010). Studies have demonstrated that long-term low-dose Pb exposure can modify the endothelium-independent relaxation response, raise the production of reactive oxygen species, and decrease the synthesis of nitric oxide (Courtois *et al.*, 2003). There was no clarification on the previous suggestion (Kim *et al.*, 2002) that the saponin chemicals in KRG could slow down hypertension. This investigation revealed that exposure to arsenic can raise blood pressure and raises the prospect that chronic KRG (100 mg/kg/day) administration may disrupt the route of the mechanism(s) causing hypertension.

In this experiment, significant haematological alterations were observed in arsenic-challenged rats. WBC, RBC, MCV, MCH, and HCT were significantly higher in the As-treated rats compared to the KRG only or As+KRG-treated animals. The current investigation demonstrated that rats treated with arsenic had abnormally low red blood cell counts and Hb values, which did not improve with KRG therapy. By interfering with the haematopoietic system, arsenic exposure results in anaemia. Arsenic significantly impairs the

activity of the enzyme delta-aminolevulinic acid dehydratase, involved in the production of heme (Gonick *et al.*, 1997; Vaziri *et al.*, 1997). Because KRG chemicals improve haematopoiesis, prolonged KRG therapy may lessen anaemia by correcting the interruption of heme production brought on by arsenic (Lee & Do, 2006).

When rats exposed to arsenic alone, the measured levels of all antioxidant compounds and enzymes were noticeably lower than in the control group reflecting oxidative stress-induced enzyme inhibition. The reduced function of superoxide dismutase and catalase observed in rats treated solely with arsenic implies that the damaging effects of free radicals surpassed the protective capabilities of these antioxidant enzymes, potentially rendering cells more vulnerable to oxidative stress. Superoxide dismutase and catalase serve as primary defenses by neutralizing superoxide radicals and breaking down harmful peroxides into benign substances (Ighodaro & Akinloye, 2018). However, when KGR was administered alongside arsenic, these levels rose in proportion to the dosage indicating partial restoration of antioxidant defense. The slight increase in catalase (8.80 mMol/min) and SOD (8040.7 U/mg protein) activities in the As+KRG treated group suggests that Korean red ginseng exerts protective effects against arsenic toxicity, possibly through its ginsenosides and phenolic constituents that scavenge reactive oxygen species (Ramesh *et al.*, 2012; Hyun *et al.*, 2022). Similarly, glutathione levels mirrored the decline seen in other antioxidants following arsenic exposure, reinforcing the likelihood of free radical-induced tissue damage. Glutathione acts as a secondary antioxidant by directly scavenging free radicals. Previous research (Jahan *et al.*,

2014; Ighodaro & Akinloye, 2018) reported comparable results and patterns.

Plasma glutathione level was drastically reduced in arsenic-induced rats. All living cells contain glutathione, a tripeptide antioxidant that aids in preventing illness and aging. It is engaged in detoxification and immune system stimulation and has a significant function in oxidation-reduction in cells (Huang *et al.*, 2022). According to the study's findings, KRG can counteract the decrease brought on by exposure to arsenic. Additionally, it was demonstrated that KRG increased the synthesis of the reduced form of glutathione, which averts oxidative damage, and that arsenic poisoning can also induce oxidative damage by lowering the plasma level of glutathione.

In this research, the hepatomarker enzymes were markedly increased in arsenic-induced rats. Liver injury is indicated by an abnormal increase in serum hepatic marker enzymes such as AST, ALT, and ALP (Park *et al.*, 2013). Serum ALP is not exclusive to hepatic impairment. On the other hand, data may indicate liver disease if elevated blood ALP is seen in conjunction with elevated serum AST and ALT values, which are more specific to liver injury. Here, interestingly, KRG inhibited AST and ALT in the arsenic exposure group. KRG extracts, on the other hand, significantly reduced the levels of serum ALT, AST, and ALP during the experiment. These findings suggest KRG extracts have a strong hepatoprotective impact against toxicity caused by arsenic. Supplementation of KRG in arsenic-exposed rats significantly reduced or restored the activity of serum creatinine and total bilirubin compared to only arsenic exposure. Also, KRG suppresses arsenic-induced triglycerides and total cholesterol. It suggested that KRG has beneficial ef-

fects on arsenic exposure and hepatic dysfunction.

In conclusion, although KRG did not affect heart rate, body weight, or white blood cell numbers, treatment with KRG significantly lowered blood pressure, raised plasma glutathione, catalase, superoxide dismutase and increased the number of red blood cells. These data indicate that treatment with KRG in arsenic-exposed groups reduced oxidative stress and lowered blood pressure suggesting that KRG might protect against arsenic-induced hypertension and oxidative stress.

ACKNOWLEDGEMENTS

This research was supported by a grant from the Korean Society of Ginseng (No: 302-168/2022), South Korea, and we also wish to express great appreciation to the Department of Veterinary and Animal Sciences, University of Rajshahi, Bangladesh, for laboratory support and the employees involved in looking after rats while performing this study.

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Paper received 05.05.2025; accepted for publication 29.07.2025

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