Intravenous Toxicity Study of Water-soluble Ginseng Pharmacopuncture in SD Rats

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Key Words
aqua acupuncture, herbal acupuncture, intravenous toxicity, radix ginseng

Abstract

Objectives: Radix Ginseng has been used for thousands of years to treat a wide variety of diseases. Radix ginseng has also been used as a traditional medicine for boosting Qi energy and tonifying the spleen and lungs. Traditionally, its effect could be obtained orally. Nowadays, a new method, the injection of herbal medicine, is being used. This study was performed to investigate the single-dose intravenous toxicity of water-soluble ginseng pharmacopuncture (WSGP) in Sprague-Dawley (SD) rats.

Methods: All experiments were carried out at Biotoxtech, an institute authorized to perform non-clinical studies under the regulation of Good Laboratory Practice (GLP). At the age of six weeks, 40 SD rats, 20 male rats and 20 female rats, were allocated into one of 4 groups according to the dosages they would receive. The WSGP was prepared in the Korean Pharmacopuncture Institute under the regulation of Korea-Good Manufacturing Practice (K-GMP). Dosages of WSGP were 0.1, 0.5 and 1.0 mL/animal for the experimental groups, and normal saline was administered to the control group. The rat’s general conditions and body weights, the results of their hematological and biochemistry tests, and their necropsy and histopathological findings were investigated to identify the toxicological effect of WSGP injected intravenously. The effect was examined for 14 days after the WSGP injection. This study was performed under the approval of the Institutional Animal Ethics Committee of Biotoxtech.

Results: No deaths were found in this single-dose toxicity test on the intravenous injection of WSGP, and no significant changes in the rat’s general conditions and body weights, the results on their hematological and biochemistry test, and their necropsy findings were observed during the test. The local area of the injection site showed minial change. The lethal dose was assumed to be over 1.0 mL/animal in both sexes.

Conclusion: These results indicate that WSGP is safe at dosages up to 1 mL/animal.

1. Introduction

Pharmacopuncture, or herbal acupuncture, is a modality of treatment that is totally different from traditionally-used methods of Korean medicine. Its therapy is derived from a combination of two traditional therapeutic methods, herbal medicine and acupuncture therapy. Pharmacopuncture treatment is performed by injecting small amounts of herbal medicinal materials at acupuncture points or affected areas in order to benefit from the effects of both herb medicine and
acupuncture [1]. In the Korean clinical environment, pharmacopuncture is frequently being used on a daily basis. Nowadays, its safety and efficacy are important issues. *Panax ginseng* (Radix ginseng, Korean ginseng) has been used as a traditional medicine for boosting Qi energy and tonifying the spleen and lungs [2]. The major important components of *Panax ginseng* are saponin glycosides known as the ginsenosides, a group of steroidal saponins. Until now, over 50 ginsenosides have been isolated from ginseng saponins [3-5]. In this research, a toxicological test on water-soluble ginseng pharmacopuncture (WSGP) was carried out.

2. Materials and Methods

WSGP was prepared in a sterile room at the Korean Pharmacopuncture Institute (Korea-Good Manufacturing Practice, K-GMP). *Panax ginseng* was carefully washed and then sliced for easier extraction. It was then placed on the bottom of the boiling pot, which was then filled with tertiary distilled water for soaking and cooking. Steam created from the ice cradle was refrigerated, and the upper layer of the distillation was then collected. The pH and the concentration of the extract were adjusted, and the extract was used after filtration, subdivision and sterilization [6].

The animals used in this study were 6-week-old Sprague-Dawley (SD) rats (Orientbio Inc., Korea). The rats were received at an age of 5 weeks, and they were kept for 1 week at room temperature. The mean weights of the rats were 189.5 — 209.2 g (male) and 145.1 — 167.6 g (female) at the time of injection. For all animals, a visual inspection was conducted; all animals were weighed using a CP3202S system (Sartorius, Germany). During the seven days of acclimatization, the general symptoms of the rats were observed once a day. The weights of the rats were recorded on the last day of acclimatization.

The temperature of the laboratory was 21.0 — 23.2°C, and the humidity was 40.9% — 59.4%. Enough food (Teklad Certified Irradiated Global 18% Protein Rodent Diet 2918C) and ultraviolet (UV)-filtered water were provided. The lights were on for 12 hours/day (from 7 am to 7 pm).

Groupings were done after seven days of acclimatization. Animals were selected if their weights were close to the mean weight. In total, 20 male rats and 20 female rats were selected. The animals were randomly distributed into 4 groups (5 male and 5 female rats per group, Table 1).

The expected volume of WSGP in clinical use is 1.0 mL per treatment. No deaths occurred in a pilot test (Biototech Study No. B12887P), so based on that study, 1.0 mL of WSGP pharmacopuncture was injected into each male and female rat in the high-dose group. The administered volume of WSGP was 0.5 mL/animal in the mid-dose group and 0.1 mL/animal in the low-dose group. One mL/animal of normal saline was administered to the rats in the control group. The administration route was intravenous because of clinical considerations. The syringe used in the experiment was a 1-mL disposable 26G syringe. The WSGP was injected at a speed of 2 mL/minutes through the tail vein. This study was conducted under the approval of the Institutional Animal Ethics Committee of Biotoxtech (No. 120896).

From the 1st day to the 14th day of treatment, the general symptoms were examined once a day. On the day of injection (day 0), the general symptoms (toxicological effects, manifestation time, recovery time, etc.), as well as mortalities, were examined at 30 minutes and 1, 2, 4, and 6 hours after injection. Body weights were measured immediately before treatment and at 3, 7 and 14 days after treatment.

After the rats had fasted for more than 18 hours after the treatment had been completed, they were anesthetized in a chamber (V-1 tabletop lab animal system, U.S.A.) filled with isoflurane gas. A blood sample was taken from the abdominal aorta on the necropsy day (15 days after injection) and was inserted into an ethylenediaminetetra – acetic acid (EDTA)-coated tube. The 1 mL of blood was analyzed by using an automatic hematology analyzer (ADVIA 120, SIEMENS, Germany). The items measured were erythrocytes (RBC), hemoglobin, hematocrits, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets (PLT), leucocytes (WBC), WBC differential counting (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and reticulocytes. A 2.0-mL blood sample was centrifuged for the blood coagulation test (3,000 rpm, 10 minutes), and serum was taken. The results were measured by using an automated coagulation analyzer (Coapresta 2000, SEKISUI, Japan). The items measured were the prothrombin time (PT) and the activated partial thromboplastin time (APTT).

Blood taken from the abdominal aorta was used in the blood biochemical test. The results were measured by using an automatic analyzer (7180, HITACHI, Japan) and an electrolyte analyzer (AVL9181, Roche, Germany). The items measured were alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), blood urea nitrogen (BUN), creatinine (Crea), total bilirubin (T-Bili), total protein (TP), albumin (Alb), albumin/globulin ratio (A/G ratio), total cholesterol (T-Chol), triglyceride (TG), phosphate (P), glucose (Glu), calcium (Ca), chloride (Cl) and potassium (K). After the termination of all observations, organs and tissues of all animals were visually inspected and were examined under a microscope after they had been stabilized by using 10% neutral buffered formalin. For the injection site, tissue slices were stained with hematoxylin & eosin (H&E).

The body weights and the results from the hematologic examinations and the blood biochemical tests were analyzed by using statistical analysis system (SAS) software (version 9.3, SAS Institute Inc., U.S.A.). The Bartlett test was conducted to evaluate the homogeneity of the variance and the significance. The significance level was 0.05. The one-way analysis of variance (ANOVA) test was conducted, and when the homogeneity of the variance was recognized, Dunnett’s t test was conducted; if homogeneity was rejected, the Kruskal-Wallis test was conducted post-hoc.
3. Results

In this study, no deaths occurred in either sex during the experiment, and no meaningful changes in body weights or abnormalities in the rats’ general conditions were noticed (Table 2). No meaningful changes in the hematological and the biochemistry tests were found. (Tables 3, 4). Also, the necropsy findings showed no abnormalities, however perivascular infiltration of inflammatory cells into the lateral vein at the injection site was observed in the male high-dose group and in the female low-dose, mid-dose and high-dose group, but those changes were minimal and seemed to be due to the injection (Table 5, Figs. 1, 2, 3, 4).

4. Discussion

Panax ginseng (Radix ginseng) has been traditionally used as an adaptogen acting on the adrenal cortex and stimulating or relaxing the nervous system to restore emotional and physical balance and to improve well-being under degenerative conditions and in old age. Its components mostly are triterpenoid saponins, panax acid, glycosides, sterols and essential oil. Trials indicate hypoglycemic, cardiovascular [7], antiviral [8], psychomotor enhancement [9], blood pressure normalization and asthma control properties. It appears to be an antioxidant and an anti-carcinogen [10, 11].

Although Ginseng (Panax ginseng) has often been used on a clinical basis for a long time, the safety of ginseng pharmacopuncture still needed to be tested. WSGP was made, and toxicity test was performed at 0.1-, 0.5-, and 1.0-mL doses of WSGP. The same doses of normal saline were administered to a control group. For the four groups, three experimental groups and one control group, neither deaths nor abnormalities in the hematological and the biochemistry tests were be found, and neither the necropsy findings nor the histopathological tests showed any abnormalities. In this study, the lethal dose 50 (LD₅₀) of WSGP was above 1.0 mL/animal in SD rats, which indicates that such a dose is safe for clinical use.

Figure 1 Tissue from a liver in the intravenous single-dose toxicity study on the injection of WSGP in SD rats.

Hematoxylin & eosin (H&E) staining (× 200, × 200) revealed no histopathological changes.
WSGP, water-soluble ginseng pharmacopuncture; SD, Sprague-Dawley.

Figure 2 Tissue from the brain in the intravenous single-dose toxicity study of WSGP in SD rats.

Hematoxylin & eosin (H&E) staining (× 200, × 200) revealed no histopathological changes.
WSGP, water-soluble ginseng pharmacopuncture; SD, Sprague-Dawley.
Figure 3 Tissue from a kidney in the intravenous single-dose toxicity study of WSGP in SD rats. Hematoxylin & eosin (H&E) staining (× 200, × 200) revealed no histopathological changes. WSGP, water-soluble ginseng pharmacopuncture; SD, Sprague-Dawley.

Figure 4 Tissue from spinal nerves in the intravenous single-dose toxicity study of WSGP in SD rats. Hematoxylin & eosin (H&E) staining (× 200, × 200) revealed no histopathological changes. WSGP, water-soluble ginseng pharmacopuncture; SD, Sprague-Dawley.

Table 1 Groups of animals

| Group                | WSGP Injection (mL/animal) | Number of animals |
|----------------------|-----------------------------|------------------|
|                      | Male | Female | Male | Female |
| G1: Control group    | 0    | 5      | 5    | 5      |
| G2: Low-dose group   | 0.1  | 5      | 5    | 5      |
| G3: Mid-dose group   | 0.5  | 5      | 5    | 5      |
| G4: High-dose group  | 1.0  | 5      | 5    | 5      |

WSGP, water-soluble ginseng pharmacopuncture.

Table 2 Mean body weights

| Sex  | Group/Dose (mL/animal) | Days after Dosing | Gain |   |
|------|------------------------|-------------------|------|---|
|      |                        | 0                 | 3    | 7 | 14 | 14 — 0 |
| Male | G1 (0)                 | 178.2 ± 6.6    | 200.6 ± 5.7 | 235.7 ± 10.2 | 297.5 ± 14.1 | 119.4 ± 15.8 |
|      | G2 (0.1)               | 179.3 ± 6.0    | 204.5 ± 7.8 | 241.5 ± 10.6 | 303.9 ± 15.4 | 124.6 ± 10.1 |
|      | G3 (0.5)               | 180.5 ± 4.5    | 205.8 ± 7.1 | 243.7 ± 8.2  | 304.8 ± 15.2 | 124.3 ± 11.3 |
|      | G4 (1.0)               | 177.7 ± 4.7    | 204.1 ± 6.8 | 242.0 ± 11.7 | 297.6 ± 19.6 | 119.8 ± 16.6 |

(Continued)
Table 3 Mean hematology parameters in male, female SD rats

| Group/Dose (mL/animal) | RBC (×10⁶ cells/µL) | HGB (g/dL) | HCT (%) | MCV (FL) | MCH (pg) | MCHC (g/dL) | PLT (× 10³ cells/µL) | Reti (%) |
|------------------------|----------------------|------------|---------|----------|----------|-------------|----------------------|---------|
| G1 (0)                 | 7.00 ± 0.20          | 14.1 ± 0.5 | 44.2 ± 1.5 | 63.2 ± 2.0 | 20.2 ± 0.8 | 32.0 ± 0.3 | 1287 ± 146          | 5.7 ± 0.7 |
| G2 (0.1)               | 6.98 ± 0.25          | 14.1 ± 0.6 | 44.2 ± 1.6 | 63.3 ± 0.4 | 20.2 ± 0.2 | 32.0 ± 0.2 | 1326 ± 67           | 6.2 ± 0.1 |
| G3 (0.5)               | 7.05 ± 0.25          | 13.8 ± 0.2 | 43.5 ± 1.1 | 61.8 ± 2.9 | 19.7 ± 0.9 | 31.8 ± 0.3 | 1348 ± 110          | 5.5 ± 0.7 |
| G4 (1.0)               | 6.82 ± 0.15          | 13.9 ± 0.4 | 43.4 ± 1.2 | 63.7 ± 1.0 | 20.4 ± 0.3 | 32.1 ± 0.5 | 1340 ± 93           | 5.5 ± 0.8 |

(Male)

| Group/Dose (mL/animal) | WBC (×10³ cells/µL) | NEU | LYM | MONO | EOS | BASO | PT (sec) | APTT (sec) |
|------------------------|---------------------|-----|-----|------|-----|------|----------|------------|
| G1 (0)                 | 7.88 ± 1.03         | 14.1 ± 6.0 | 81.5 ± 6.0 | 2.4 ± 0.5 | 0.4 ± 0.1 | 0.2 ± 0.1 | 17.0 ± 0.7 | 13.0 ± 1.8 |
| G2 (0.1)               | 8.67 ± 2.26         | 15.1 ± 3.5 | 80.5 ± 2.7 | 2.4 ± 0.5 | 0.4 ± 0.1 | 0.2 ± 0.1 | 16.8 ± 0.9 | 12.2 ± 1.5 |
| G3 (0.5)               | 8.01 ± 3.20         | 15.8 ± 3.0 | 79.6 ± 3.2 | 2.6 ± 0.6 | 0.6 ± 0.3 | 0.2 ± 0.1 | 17.4 ± 0.6 | 14.5 ± 0.9 |
| G4 (1.0)               | 8.48 ± 2.05         | 13.1 ± 5.4 | 83.1 ± 5.5 | 1.9 ± 0.6 | 0.4 ± 0.1 | 0.2 ± 0.1 | 17.2 ± 0.4 | 14.7 ± 1.3 |

(Female)

| Group/Dose (mL/animal) | RBC (×10⁶ cells/µL) | HGB (g/dL) | HCT (%) | MCV (FL) | MCH (pg) | MCHC (g/dL) | PLT (× 10³ cells/µL) | Reti (%) |
|------------------------|----------------------|------------|---------|----------|----------|-------------|----------------------|---------|
| G1 (0)                 | 7.32 ± 0.43          | 14.2 ± 0.6 | 43.4 ± 1.8 | 59.4 ± 2.2 | 19.5 ± 0.7 | 32.8 ± 0.6 | 1281 ± 77           | 2.9 ± 1.1 |
| G2 (0.1)               | 7.33 ± 0.26          | 14.5 ± 0.5 | 44.1 ± 1.4 | 60.2 ± 1.5 | 19.8 ± 0.6 | 33.0 ± 0.2 | 1235 ± 119          | 2.9 ± 0.5 |
| G3 (0.5)               | 7.59 ± 0.22          | 15.0 ± 0.4 | 45.7 ± 0.7 | 60.3 ± 2.1 | 19.8 ± 0.8 | 32.9 ± 0.4 | 1375 ± 154          | 3.2 ± 0.4 |
| G4 (1.0)               | 7.48 ± 0.24          | 14.4 ± 0.7 | 44.1 ± 2.0 | 59.0 ± 1.1 | 19.3 ± 0.4 | 32.8 ± 0.1 | 1242 ± 120          | 2.9 ± 0.6 |

| Group/Dose (mL/animal) | WBC (×10³ cells/µL) | NEU | LYM | MONO | EOS | BASO | PT (sec) | APTT (sec) |
|------------------------|---------------------|-----|-----|------|-----|------|----------|------------|
| G1 (0)                 | 4.27 ± 1.00         | 20.0 ± 5.3 | 75.6 ± 5.4 | 2.1 ± 0.8 | 1.3 ± 0.5 | 0.1 ± 0.0 | 18.6 ± 1.6 | 13.3 ± 1.4 |
| G2 (0.1)               | 3.63 ± 1.56         | 16.8 ± 8.1 | 79.5 ± 7.6 | 1.7 ± 0.9 | 1.0 ± 0.6 | 0.1 ± 0.0 | 18.6 ± 0.6 | 14.5 ± 1.0 |
| G3 (0.5)               | 4.36 ± 1.30         | 19.0 ± 4.3 | 77.1 ± 4.4 | 2.0 ± 0.4 | 0.8 ± 0.5 | 0.1 ± 0.1 | 17.9 ± 1.1 | 15.6 ± 1.9 |
| G4 (1.0)               | 4.26 ± 1.98         | 14.2 ± 4.7 | 82.3 ± 4.7 | 1.7 ± 0.6 | 0.9 ± 0.5 | 0.1 ± 0.1 | 18.3 ± 0.6 | 14.2 ± 1.6 |

SD, Sprague-Dawley; RBC, red blood cell; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PLT, platelets; Reti, reticulocytes; PT, prothrombin time; APTT, activated partial thromboplastin time; RBC, red blood cell; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PLT, platelet; Reti, reticulocytes; PT, prothrombin time; APTT, activated partial thromboplastin time.
Table 4 Mean clinical chemistry in male, female SD rats
(Male)

| Group/Dose (mL/animal) | ALT (U/L) | AST (U/L) | ALP (U/L) | GGT (U/L) | Glu (mg/dL) | BUN (mg/dL) | Crea (mg/dL) | T-Bili (mg/dL) | T-Chol (mg/dL) |
|------------------------|-----------|-----------|-----------|-----------|-------------|-------------|-------------|----------------|----------------|
| G1 (0)                 | 23.4 ± 1.3| 85.9 ± 12.6| 831.2 ± 162.0| 0.39 ± 0.14| 144 ± 16 | 11.2 ± 1.7 | 0.37 ± 0.03 | 0.01 ± 0.01 | 71 ± 11 |
| G2 (0.1)               | 26.8 ± 3.1| 79.2 ± 4.8 | 805.4 ± 159.6| 0.28 ± 0.10| 133 ± 9 | 10.7 ± 1.6 | 0.37 ± 0.02 | 0.03 ± 0.01 | 80 ± 12 |
| G3 (0.5)               | 24.8 ± 2.0| 88.7 ± 19.4| 786.0 ± 159.0| 0.42 ± 0.06| 135 ± 16 | 11.1 ± 1.6 | 0.37 ± 0.02 | 0.02 ± 0.01 | 86 ± 18 |
| G4 (1.0)               | 25.7 ± 4.2| 77.3 ± 20.8| 893.4 ± 164.6| 0.42 ± 0.14| 145 ± 18 | 10.8 ± 1.3 | 0.37 ± 0.03 | 0.03 ± 0.01 | 84 ± 19 |

| Group/Dose (mL/animal) | TG (mg/dL) | TP (g/dL) | Alb (g/dL) | A/G ratio | P (mg/dL) | Ca (mg/dL) | Na (mmol/L) | K (mmol/L) | Cl (mmol/L) |
|------------------------|------------|-----------|------------|------------|------------|------------|-------------|------------|-------------|
| G1 (0)                 | 39 ± 10    | 5.2 ± 0.1 | 2.3 ± 0.1  | 0.76 ± 0.03| 8.92 ± 0.32| 9.8 ± 0.2 | 140 ± 1     | 4.9 ± 0.3 | 104 ± 1     |
| G2 (0.1)               | 47 ± 11    | 5.3 ± 0.1 | 2.4 ± 0.1  | 0.80 ± 0.05| 8.81 ± 0.15| 10.0 ± 0.4| 140 ± 2     | 4.8 ± 0.4 | 103 ± 1     |
| G3 (0.5)               | 44 ± 17    | 5.1 ± 0.2 | 2.2 ± 0.1  | 0.77 ± 0.01| 8.63 ± 0.36| 9.8 ± 0.4 | 139 ± 2     | 4.9 ± 0.4 | 104 ± 2     |
| G4 (1.0)               | 46 ± 25    | 5.2 ± 0.0 | 2.2 ± 0.1  | 0.76 ± 0.07| 9.05 ± 0.24| 10.0 ± 0.4| 139 ± 1     | 4.9 ± 0.3 | 102 ± 1     |

(Female)

| Group/Dose (mL/animal) | ALT (U/L) | AST (U/L) | ALP (U/L) | GGT (U/L) | Glu (mg/dL) | BUN (mg/dL) | Crea (mg/dL) | T-Bili (mg/dL) | T-Chol (mg/dL) |
|------------------------|-----------|-----------|-----------|-----------|-------------|-------------|-------------|----------------|----------------|
| G1 (0)                 | 23.2 ± 5.7| 111.3±40.1| 484.1±102.8| 0.55±0.22 | 111±17     | 12.6±0.7   | 0.40±0.04   | 0.04±0.03   | 81±21 |
| G2 (0.1)               | 20.9 ± 2.0| 85.9±10.0 | 635.3±129.1| 0.64±0.13 | 118±10     | 12.2±1.7   | 0.38±0.04   | 0.02±0.01   | 81±13 |
| G3 (0.5)               | 18.5 ± 1.4| 76.6±22.1 | 563.9±134.6| 0.60±0.20 | 134±24     | 12.7±0.8   | 0.39±0.02   | 0.02±0.01   | 86±13 |
| G4 (1.0)               | 18.9 ± 1.7| 77.4±14.1 | 610.4±181.2| 0.66±0.25 | 117±13     | 13.2±1.3   | 0.41±0.04   | 0.02±0.01   | 88±23 |

| Group/Dose (mL/animal) | TG (mg/dL) | TP (g/dL) | Alb (g/dL) | A/G ratio | P (mg/dL) | Ca (mg/dL) | Na (mmol/L) | K (mmol/L) | Cl (mmol/L) |
|------------------------|------------|-----------|------------|------------|------------|------------|-------------|------------|-------------|
| G1 (0)                 | 21 ± 25    | 5.6 ± 0.2 | 2.5 ± 0.1  | 0.81 ± 0.04| 7.19 ± 0.63| 9.6 ± 0.3 | 140 ± 2     | 4.8 ± 0.2 | 105 ± 1     |
| G2 (0.1)               | 11 ± 2     | 5.4 ± 0.2 | 2.4 ± 0.0  | 0.82 ± 0.05| 7.66 ± 0.32| 9.6 ± 0.1 | 140 ± 2     | 4.8 ± 0.4 | 105 ± 1     |
| G3 (0.5)               | 15 ± 4     | 5.5 ± 0.2 | 2.5 ± 0.1  | 0.83 ± 0.02| 7.79 ± 0.34| 9.8 ± 0.3 | 140 ± 2     | 4.5 ± 0.2 | 107 ± 2     |
| G4 (1.0)               | 13 ± 2     | 5.5 ± 0.3 | 2.6 ± 0.2  | 0.87 ± 0.06| 7.47 ± 0.73| 9.8 ± 0.4 | 140 ± 1     | 4.6 ± 0.3 | 106 ± 1     |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, glutamyl transpeptidase; Glu, glucose; BUN, blood urea nitrogen; Crea, creatinine; T-Bili, total bilirubin; A/G gamma ratio, albumin globulin ratio; P, phosphorus; Ca, calcium; Na, sodium; K, potassium; Cl, chloride.

Table 5 Summary of histopathological findings

| Sex | Male | Female |
|-----|------|--------|
| Organ / Findings | Group/Dose (mL/animal) | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| No. of animals | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

(Continued)
### 5. Conclusion

The results of administering WSGP via a venous route did not cause any changes in weight development, in the hematological and the biochemical tests or in the necropsy findings. In addition, no deaths were observed. These results indicate that venous administration of WSGP is a safe modality of treatment.

### Conflict of interest

The authors declare that there are no conflict of interest.

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