

**Institute of Nutrition and Food Safety
Chinese Center for Disease Control and Prevention**

Laboratory Testing Report

Report No.: 20030201

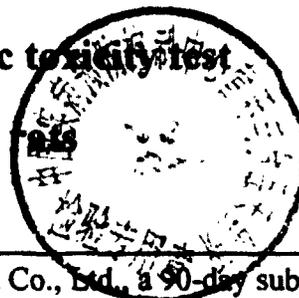
Name of Sample: Xiwang capsule

Source of Sample: Shanghai Stone Nano Technology Port Co., LTD.

Date of Issue: _____



Report on a 90-day subchronic toxicity test on Xiwang capsule in rats



Commissioned by Shanghai Stone Nano-tech Port Co., Ltd., a 90-day subchronic test in rats using Xiwang capsule was conducted by the Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention. Xiwang capsule is a new selenium-contained functional food and the chemical form of its selenium is nanometer selenium, which is different from the inorganic selenium and organic selenium. In this study, the subchronic toxicity of Xiwang capsule was compared with sodium selenite (inorganic selenium) and selenoprotein (organic selenium).

Materials and Methods

1. Materials

1.1 Test samples

Xiwang capsule was provided by Shanghai Stone Nano-tech Port Co., Ltd. The compound was in the form of orange powder, and its selenium concentration was 184 mg/kg. Selenoprotein was prepared from selenium rich soybeans produced in Enshi, Hubei Province and the selenium concentration was 149 mg/kg. The analytical data of selenium in Xiwang capsule and selenoprotein were provided by the Department of Trace Element, Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention and the 2,3-diaminonaphtholin fluorescence method ⁽¹⁾ was used to determine the selenium concentration. Sodium selenite was purchased from Beijing Chemical Factory and its selenium concentration was 45.7%.

1.2 Animals and diets

SD rats and basal diets were obtained from Beijing Research Center for Experimental Animals and the Institute of Experimental Zoology, Chinese Academy of Medical Sciences, respectively.

2. Methods

Three hundred and twelve healthy weaning SD rats (60-80 g body weight) were randomly divided into 13 groups. Each group consisted of 12 males and 12 females. The negative control group was given basal diets; Groups A2 to A5 were given diets with Xiwang capsule which contained 2, 3, 4 and 5 ppm selenium, respectively; Groups B2 to B5 were given diets with selenoprotein which contained 2, 3, 4 and 5 ppm selenium, respectively; Groups C2 to C5 were given diets with sodium selenite which contained 2, 3, 4 and 5 ppm selenium, respectively. Samples were added to the basal diet to reach the corresponding selenium concentration (2, 3, 4 or 5 ppm). Rats were kept in individual cages and free access to food and water. The animals were maintained in a controlled environment at $24 \pm 1^\circ\text{C}$ and $50 \pm 10\%$ relative humidity

with the altering 12:12-hour light-dark cycle. Rats were fed with the above diets for 90 days.

3 Parameters examined

3.1 Body weight and food efficiency: Food consumption and body weights were measured weekly to calculate the total body weight gain, total food consumption and food efficiency (body weight gain/100 g diet).

3.2 Hematology tests: The tests were performed in the middle of the study (day 45) and at the end of the study. The hematological parameters included hemoglobin, red cell count, total white cell count and white cell differential count, and platelet count.

3.3 Clinical chemistry tests: In the middle of the study (day 45) and at the end of the study, blood samples were obtained from the orbital plexus of rats and serum was separated by centrifugation (3,000 rpm/minute for 15 minutes). Model 7060 autoanalyzer (Hitachi) and respective test kits from Chinese Biology Engineering Hitech Company were used to analyze the following parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (ALB), glucose (GLU), urea nitrogen (BUN), creatinine (Cre), total cholesterol (T-Che) and triglyceride (TG).

3.4 Organ weights and body weight ratio: At the end of the experiment, animals were sacrificed after recording the body weights. The weight of liver, kidneys, spleen, heart, brain and testis were measured to calculate the organ and body weight ratio.

3.5 Histopathological examination: At the end of the experiment, animals were sacrificed. Rats were dissected for macroscopic examination first, then, tissues including liver, kidney, spleen, stomach and intestine, testis (ovary), brain, pituitary, heart, thyroids, pancreas and adrenals were fixed in 10% formaldehyde solution, and embedded in paraffin wax. Tissue sections were stained with Hematoxylin-Eosin and examined under microscope.

4 Statistical analysis

Means and standard deviations of the data were calculated by Excel software and analyzed by PEMS software package.

Results and Discussion

1 General conditions and food efficiency

The animals in all groups were in good condition. No overt toxic effects were observed.

The results of body weight were shown in Tables 1-4. Compared with the negative control group, the body weights of male rats in 4 and 5 ppm Xiwang capsule-treated groups were decreased significantly from week 8 to week 11 and from week 8 to week13, respectively. The body weights of males in 4 and 5 ppm sodium selenite-treated groups were decreased significantly from week 5 to week 13 and from week3 to week13, respectively. The body weights of males in 3, 4 and 5 ppm seleoprotein-treated groups were decreased significantly from week 6 to week 10,

from week 4 to week13 and from week 4 to week13, respectively. The body weights of females in 4 and 5 ppm Xiwang capsule-treated groups were significantly lower than the controls from week 6 to week 8 and from week 5 to week13, respectively. The body weights of females in 3, 4 and 5 ppm sodium selenite-treated groups were decreased significantly from week 4 to week 13, from week 4 to week 13 and from week 3 to week13, respectively. The body weights of females in 3, 4 and 5 ppm seleoprotein-treated groups were decreased significantly from week 4 to week 13, from week 5 to week13 and from week 3 to week13, respectively.

The results of total body weight gain and total food efficiency were shown in Table 5. Total body weight gain of males and females and total food efficiency of males in 5 ppm Xiwang capsule-treated group were significantly lower than the controls. Total body weight gain of females in 3 ppm selenite-treated group and total food efficiency of males and females in 4 and 5 ppm selenite-treated groups were significantly lower than the controls. Total body weight gain of males in 4 and 5 ppm selenoprotein-treated groups and females in 3, 4 and 5 ppm selenoprotein-treated groups, and total food efficiency of males in 5 ppm selenoprotein -treated groups were significantly lower than the controls.

The above results showed that the non-observed-adverse-effect-level (NOAEL) of Xiwang capsule on body weight gain and food efficiency of male and female rats was 4 ppm selenium (0.4 mg/kg bw). On the other hand, the NOAEL of sodium selenite and selenoprotein on male and female rat were 3 ppm selenium (0.3 mg/kg BW) and 2 ppm selenium (0.2 mg/kg BW), respectively.

2 Hematology

Results in the middle of the study were shown in Tables 6 and 7. Hemoglobin and red cell count in males of 5 ppm Xiwang capsule, sodium selenite and selenoprotein-treated groups were significantly lower than the controls. Platelet count in males of 5 ppm sodium selenite and selenoprotein-treated groups is significantly lower than the controls. No significant differences were found in other parameters. For females, there were no significant differences between the Xiwang-treated groups and the controls. Hemoglobin, red cell count and platelet count in rats of 5 ppm sodium selenite-treated groups were significantly lower than the controls. Hemoglobin and red cell count of rats in 4 and 5 ppm selenoprotein-treated groups and platelet count in rats of 5 ppm selenoprotein-treated groups were significantly lower than the controls. No significant differences were found in other parameters.

The results at the end of the study were shown in Tables 8 and 9. Hemoglobin and red cell count in males of 5 ppm Xiwang capsule and selenoprotein-treated groups were significantly lower than the controls. Red cell count and platelet count of rats in 4 ppm sodium selenite-treated groups and hemoglobin, red cell count and platelet count in rats of 5 ppm sodium selenite-treated groups were significantly lower than the controls. For females, there were no significant differences between the Xiwang-treated groups and the controls. Hemoglobin and platelet count of rats in 4 ppm sodium selenite -treated groups and hemoglobin, red cell count and platelet count in rats of 5 ppm sodium selenite -treated groups were significantly lower than the controls. Hemoglobin of rats in 4 and 5 ppm selenoprotein-treated groups and red cell

count in rats of 5 ppm selenoprotein-treated groups were significantly lower than the controls.

It is concluded from above results that 5 ppm selenium from Xiwang capsule significantly decreased hemoglobin and red cell count in males, while no adverse effects of Xiwang capsule on hematology in females were observed; 4 ppm selenium from sodium selenite significantly decreased red cell count of males, hemoglobin of females and platelet count of males and females, and 5 ppm selenium from sodium selenite significantly decreased hemoglobin, red cell count and platelet count of males and females; 4 ppm selenium from selenoprotein significantly decreased hemoglobin and red cell count of females, and 5 ppm selenium from selenoprotein significantly decreased hemoglobin, red cell count and platelet count of males and females .

Therefore, the NOAEL of Xiwang capsule on hematology of males and females were 4 ppm selenium (0.4 mg/kg bw) and 5 ppm selenium (0.5 mg/kg bw), respectively. The NOAEL of sodium selenite on hematology of males and females were 3 ppm selenium (0.3 mg/kg bw). The NOAEL of selenoprotein on hematology of males and females were 4 ppm selenium (0.4 mg/kg bw) and 3 ppm selenium (0.3 mg/kg bw), respectively.

3 Clinical chemistry

The results in the middle of the study were shown in Tables 10 and 11. For male rats, no adverse effects of Xiwang capsule on clinical chemistry were observed. ALT activity in 5 ppm sodium selenite-treated group was significantly higher than the controls, and the ALB level was significantly lower than the controls. ALT and AST activities in 5 ppm selenoprotein-treated group were significantly higher than the controls, and the TP and ALB level were significantly lower than the controls. For female rats, ALT activity in 5 ppm Xiwang capsule-treated group was significantly higher than the controls, and TP and ALB level were significantly lower than the controls. ALT activity in 4 and 5 ppm sodium selenite-treated groups was significantly higher than the controls, and TP and ALB level in 5 ppm sodium selenite-treated group were significantly lower than the controls. ALT activity in 4 and 5 ppm selenoprotein-treated groups was significantly higher than the controls, and TP and ALB level were significantly lower than the controls. No significant differences were found in other parameters.

The results at the end of the study were shown in Tables 12 and 13. For male rats, ALT activity in 5 ppm sodium Xiwang capsule-treated group was significantly higher than the controls. ALT activity in 4 and 5 ppm sodium selenite-treated groups were significantly higher than the controls. ALT and AST activities in 5 ppm selenoprotein-treated group were significantly higher than the controls. For female rats, ALT activity in 5 ppm Xiwang capsule-treated group was significantly higher than the controls. ALT activity in 5 ppm sodium selenite-treated groups was significantly higher than the controls, and TP and ALB levels in 4 and 5 ppm sodium selenite-treated group were significantly lower than the controls. ALT activity in 4 and 5 ppm selenoprotein-treated groups and AST activity in 5 ppm selenoprotein-treated group were significantly higher than the controls, and TP and ALB level in 5 ppm selenoprotein-treated groups were significantly lower than the controls. No significant

differences were observed in other parameters between the selenium-treated groups and the control group.

Liver is the main target organ of the selenium compound toxicity, which is indicated by increased ALT and AST activities and decreased the liver protein synthesis ability, thus decreasing TP and ALB levels. 5 ppm selenium from Xiwang capsule significantly increased ALT activity of males and females, and significantly decreased TP and ALB level of females. 4 and 5 ppm selenium from sodium selenite significantly increased ALT activity of male and females and decreased TP and ALB level of females, and 5 ppm selenium from sodium selenite significantly decreased ALB level of males. 4 ppm selenium from selenoprotein significantly increased ALT activity of females and significantly decreased TP and ALB level of females. 5 ppm selenium from selenoprotein significantly increased ALT and AST activities of males and females and significantly decreased TP and ALB level of males and females.

Therefore, the NOAEL of Xiwang capsule on clinical chemistry of males and females was 4 ppm selenium (0.4 mg/kg bw). The NOAEL of sodium selenite on clinical chemistry of males and females was 3ppm selenium (0.3 mg/kg bw). The NOAEL of selenoprotein on clinical chemistry of males and females was 4 ppm selenium (0.4 mg/kg bw) and 3 ppm selenium (0.3 mg/kg bw), respectively.

4 Organ weight and body weight ratio (the relative weight)

The results were shown in Tables 14 and 15. The relative liver, spleen, brain, and heart weight of males in 5 ppm Xiwang capsule-treated group were significantly higher than the controls. The relative liver, spleen, and heart weight of males in 4 ppm and 5 ppm sodium selenite-treated groups and the relative brain weight in 5 ppm sodium selenite-treated group were significantly higher than the controls. The relative liver, kidney, testis and brain weight of males in 4 ppm selenoprotein-treated group and the relative liver, kidney, spleen, testis, brain and heart weight in 5 ppm seleprotein-treated group were significantly higher than the controls.

The relative liver, spleen and heart weight of females in 5 ppm Xiwang capsule-treated group were significantly higher than the controls. The relative liver and spleen weight of females in 4 ppm sodium selenite-treated group and the relative liver, kidney, spleen and heart weight in 5 ppm sodium selenite-treated group were significantly higher than the controls. The relative liver weight of females in 3 ppm selenoprotein-treated group, the relative liver and brain weight of females in 4 ppm selenoprotein-treated group and the relative liver, kidney, spleen, brain and heart weight in 5 ppm seleprotein-treated group were significantly higher than the controls.

Therefore, the NOAELs of Xiwang capsule on the relative weight of males and females were 4 ppm selenium (0.4 mg/kg bw). The NOAELs of sodium selenite were 3 ppm selenium (0.3 mg/kg bw) for males and females. The NOAELs of selenoprotein were 3 ppm selenium (0.3 mg/kg bw) for males and 2 ppm selenium (0.2 mg/kg bw) for females.

5 Histopathology

The results were shown in Tables 16 and 17. Grossly, various grades of hepatic nodules and rough surface were observed in 4 ppm and 5 ppm Xiwang capsule, sodium selenite and selenoprotein-treated groups, no abnormalities were observed in

other groups. The incidence of hepatic nodules of females in 4 ppm and 5 ppm Xiwang capsule-treated groups was significantly lower than those in sodium selenite and selenoprotein-treated groups. The incidence of hepatic nodules of males in 5 ppm Xiwang capsule-treated group was lower than those in sodium selenite and selenoprotein-treated groups, but significant difference was found between Xiwang capsule and selenoprotein-treated groups. The number of rough surface in 4 ppm Xiwang capsule-treated group was lower than those in sodium selenite and selenoprotein-treated groups, but no significant differences were observed.

Histopathologically, typical liver lesions observed included liver structure disturbance or damage, hepatic nodules, different degrees of vacuolar degeneration in liver cytoplasm and small biliary duct and fibroplastic proliferation in liver portal area in some rats of the three selenium-treated groups. The results were shown in Table 17. The liver structure was normal in rats of 3 ppm Xiwang capsule-treated groups, while liver structure disturbance was observed in some rats of sodium selenite-treated groups (five out of 12 females and three out of 12 males) and selenoprotein-treated groups (three out of 12 females and three out of 12 males). The incidence of liver disturbance and damage in males of 4 ppm Xiwang capsule-treated group (8 out of 12) was significantly lower than that of sodium selenite (12 out of 12) and selenoprotein (12 out of 12). The incidence of liver damage in females of 4 ppm Xiwang capsule-treated group (3 out of 12) was significantly lower than that of sodium selenite (8 out of 12) and selenoprotein (11 out of 12). The incidence of liver damage in males and females of 5 ppm Xiwang capsule-treated group (4 out of 12 males and 3 out of 12 females) was significantly lower than that of sodium selenite (11 out of 12 males and 9 out of 12 females) and selenoprotein (12 out of 12 males and 10 out of 12 females). In addition, teniform or patchy necrosis in epithelial cells of kidney medulla was observed in some rats of 5 ppm sodium selenite (4 out of 24 rats) and selenoprotein (4 out of 24 rats) treated groups. No any kidney pathological changes were observed in rats of Xiwang capsule-treated group. No any pathological changes were found in other organs. In summary, no pathological changes were found in rats of 3 ppm Xiwang capsule-treated groups. The degree of histopathological changes in rats of 4 and 5 ppm Xiwang capsule-treated groups was lower than sodium selenite and selenoprotein. No any pathological changes of kidney were found in rats of Xiwang capsule-treated group.

The NOAELs of Xiwang capsule on histopathological changes were 3 ppm (0.3 mg/kg BW) for males and females and the NOAELs of sodium selenite and selenoprotein were 2 ppm (0.2 mg/kg BW) for males and females.

Conclusions (Table 18)

1. Xiwang capsule, sodium selenite and selenoprotein at high dose (5 ppm, 0.5 mg/kg bw) all decreased body weight gain in rats. The NOAEL of Xiwang capsule on body weight were 4 ppm (0.4 mg/kg bw), and the NOAEL of sodium selenite and selenoprotein on body weight were 3 ppm (0.3 mg/kg bw) for males

and 2 ppm (0.2 mg/kg bw) for females, respectively, Therefore, the body weight gain decrease caused by Xiwang capsule was less strong than those caused by selenoprotein and sodium selenite.

2. Xiwang capsule, selenoprotein and sodium selenite at high dose all decreased hemoglobin, red cell count and platelet count in rats. The NOAEL of Xiwang capsule on hematology was 4 ppm (0.4 mg/kg bw) for males and 5 ppm (0.5 mg/kg bw) for females. The NOAELs of sodium selenite were 3 ppm (0.3 mg/kg bw) for males and females. The NOAELs of selenoprotein were 4 ppm (0.4 mg/kg bw) for males and 3 ppm (0.3 mg/kg bw) for females. Therefore, the decrease of hematology indicators caused by Xiwang capsule was less strong than those caused by selenoprotein and sodium selenite.
3. Liver was the main target organ of the selenium compound toxicity which caused increased ALT and AST activities and decreased liver protein synthesis ability, thus decreasing TP and ALB level. The NOAEL of Xiwang capsule on clinical chemistry was 4 ppm (0.4 mg/kg bw) for both males and females. The NOAELs of sodium selenite were 3 ppm (0.3 mg/kg bw) for both males and females. The NOAELs of selenoprotein were 4 ppm (0.4 mg/kg bw) for males and 3 ppm (0.3 mg/kg bw) for females. Therefore, the toxicity of Xiwang capsule to liver was lower than selenoprotein and sodium selenite.
4. Xiwang capsule, selenoprotein and sodium selenite at high doses increased the relative organ weight of rats. The NOAELs of Xiwang capsule on the relative organ weight were 4 ppm (0.4 mg/kg bw) for males and females. The NOAELs of sodium selenite were 3 ppm (0.3 mg/kg bw) for males and females. The NOAELs of selenoprotein were 3 ppm for males and 2 ppm (0.2 mg/kg bw) for females.
5. Different degrees of liver lesions were observed in some rats of three selenium-treated groups, however, the degree of lesions induced by Xiwang capsule was significantly lower than sodium selenite and selenoprotein. The NOAEL of Xiwang capsule on liver histopathological changes was 3 ppm (0.3 mg/kg BW) and the NOAELs of sodium selenite and selenoprotein were 2 ppm (0.2 mg/kg BW). Kidney lesions were found in some rats of 5 ppm sodium selenite and selenoprotein-treated groups, while no kidney pathological changes were found in rats of Xiwang capsule-treated group.

In conclusion, if the effect of selenium on the growth, hematology and clinical chemistry was assessed comprehensively, the NOAEL of Xiwang capsule was 4 ppm (0.4 mg/kg bw) for both male and female rats, and the NOAELs of sodium selenite and selenoprotein were 3 ppm (0.3 mg/kg bw) for males and 2 ppm (0.2 mg/kg bw) for females. If the effect of selenium on the histopathological changes of liver was used as the end point, the NOAEL of Xiwang capsule was 3 ppm (0.3 mg/kg bw) for both male and female rats, and the NOAELs of sodium selenite and selenoprotein were 2 ppm (0.2 mg/kg bw) for males and females. All in all, the toxicity of selenium from Xiwang capsule was lower than sodium selenite and selenoprotein.

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Reference

1 Wang GY, Liu SJ, Yang GQ, et al. Fluorescence determination of selenium in biological preparations, water and the soil. *Acta Nutrimenta Sinica*, 1985. 7(1):39-45.

Table1 The effects of Xiwang capsule, sodium selenite and selenoprotein on body weight of male rats

Groups	No. of rats	Week0	Week1	Week2	Week3	Week4	Week5	Week6
A2	12	64.4±4.5	109.5±6.6	166.9±14.6	227.0±16.5	293.8±21.3	332.5±28.6	375.8±31.6
A3	12	64.4±4.8	113.3±11.8	166.4±13.3	224.8±18.8	273.1±20.0	319.8±30.3	355.8±25.7
A4	12	64.3±5.3	110.9±11.4	163.2±12.9	218.8±19.8	284.8±23.3	335.4±26.4	361.8±25.8
A5	12	64.8±10.4	107.8±10.4	156.4±20.0	218.8±27.5	283.7±32.5	331.3±33.3	361.3±37.7
B2	12	64.4±5.5	109.8±8.9	159.8±10.9	211.4±17.3	279.5±16.3	339.6±17.0	370.6±18.5
B3	12	64.4±4.7	112.4±7.4	164.3±9.8	227.3±12.6	280.8±15.8	334.3±19.2	369.9±21.8
B4	12	64.6±4.0	116.3±8.5	160.2±11.0	213.1±16.5	276.3±13.8	283.2±19.2**	300.1±17.5*
B5	12	64.4±7.3	113.6±11.0	160.6±12.6	184.8±24.9**	209.0±29.3**	232.6±34.1**	269.6±35.3**
C2	12	64.4±4.5	110.8±7.4	165.3±9.0	226.5±13.1	291.8±17.4	347.2±22.9	388.8±27.1
C3	12	64.4±7.8	118.3±9.9	163.2±21.0	221.9±21.7	283.6±29.7	327.9±33.0	350.1±36.4*
C4	12	64.3±7.5	113.8±9.3	158.8±13.7	214.8±20.8	258.8±19.1**	277.8±21.8**	298.4±30.2**
C5	12	64.3±5.8	110.1±14.3	161.5±13.2	205.6±18.2	248.8±20.2**	268.2±23.5**	276.3±25.6**
Control	12	64.4±5.8	116.2±8.6	168.1±11.0	223.6±18.6	292.4±26.0	341.5±30.0	381.6±39.9

Notes: A2- A5: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B2-B5: 2, 3, 4 and 5ppm sodium selenite-treated groups; C2-C5: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls.

Table 2 The effects of Xiwang capsule, sodium selenite and selenoprotein on body weight of male rats

Groups	No. of rats	Week7	Week8	Week9	Week10	Week11	Week12	Week13
A2	12	408.9±31.0	438.2±34.6	461.6±37.5	469.2±31.8	488.0±33.8	497.5±38.0	507.3±51.2
A3	12	383.4±26.9	413.6±24.7	426.7±30.8	435.8±36.2	451.1±43.3	467.6±47.8	477.0±52.0
A4	12	380.3±25.3	390.0±24.3*	399.2±37.3**	419.9±39.0**	437.9±38.6**	461.1±43.2	478.6±42.9
A5	12	379.5±38.6	386.9±38.3*	393.5±38.0**	396.8±34.4**	404.2±35.0**	416.6±39.1*	429.5±41.4**
B2	12	392.3±20.6	422.9±20.4	446.0±24.1	467.1±23.4	484.0±26.4	495.9±25.9	506.5±32.3
B3	12	392.6±22.5	418.9±22.2	425.8±29.3	448.9±29.7	463.1±29.1	484.8±37.9	495.9±38.9
B4	12	392.8±25.3**	356.3±30.1**	372.7±36.4**	388.3±47.8**	402.9±51.1**	429.3±53.2**	445.1±57.1**
B5	12	295.9±43.1**	327.8±45.2**	348.9±53.8**	364.7±55.6**	386.3±60.6**	397.0±64.0**	414.3±70.5**
C2	12	407.3±26.9	429.8±30.2	447.0±29.6	462.1±43.1	479.8±44.5	483.0±46.1	502.7±48.8
C3	12	364.8±37.7*	384.0±44.2*	413.6±40.5*	429.6±37.9*	452.9±46.7	477.7±45.5	484.1±50.8
C4	12	333.6±35.4**	357.2±37.1**	382.6±36.5**	404.1±38.1**	418.4±39.3**	438.9±46.3**	446.7±39.3**
C5	12	281.3±24.2**	292.0±28.9**	320.5±31.0**	340.2±33.9**	364.5±42.1**	387.0±53.7**	399.6±60.1**
Control	12	403.3±44.5	431.1±47.8	451.1±50.0	470.8±51.2	493.1±51.7	504.5±54.0	512.7±54.6

Notes: A2- A5: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B2-B5: 2, 3, 4 and 5ppm sodium selenite-treated groups; C2-C5: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls.

Table3 The effects of Xiwang capsule, sodium selenite and selenoprotein on body weight of female rats

Groups	No. of rats	Week0	Week1	Week2	Week3	Week4	Week5	Week6
A2	12	62.4±5.9	102.2±8.0	139.2±9.3	165.8±9.2	196.0±10.5	214.9±11.2	228.1±12.5
A3	12	62.5±7.3	104.5±10.1	139.3±9.4	166.2±11.9	193.3±16.7	209.3±14.7	224.2±15.4
A4	12	62.6±6.6	106.1±8.8	149.6±11.9	173.0±11.6	196.0±10.9	211.8±12.2	217.6±16.4**
A5	12	62.6±5.3	100.8±7.5	139.3±14.7	166.0±14.5	192.5±13.7	201.2±12.1**	209.5±14.6**
B2	12	62.8±6.2	102.3±8.4	141.8±12.5	170.1±13.5	198.8±13.5	216.9±16.6	231.7±17.0
B3	12	62.6±3.9	104.8±5.5	146.9±11.1	167.2±11.2	174.3±11.6**	189.6±14.6**	207.3±15.5**
B4	12	62.1±8.3	99.3±7.8	139.9±10.0	166.3±13.2	175.8±12.4**	185.5±14.3**	203.1±15.7**
B5	12	62.8±7.2	102.9±11.6	139.8±13.3	152.3±15.5**	169.9±15.2**	178.1±17.5**	192.5±12.3**
C2	12	62.7±6.6	103.2±9.2	137.4±14.2	167.3±11.1	198.7±13.8	214.1±12.6	229.3±12.2
C3	12	62.8±5.4	102.5±9.0	145.1±14.6	161.7±15.8	180.8±18.6*	198.2±19.2**	211.8±19.4**
C4	12	62.8±4.8	106.8±8.2	138.6±8.4	160.1±15.3	187.3±18.5	193.9±19.3**	200.6±17.2**
C5	12	62.7±5.6	107.9±8.7	137.8±9.5	152.3±12.1**	161.3±12.1**	167.5±16.4**	177.1±17.4**
Control	12	62.7±5.5	104.5±6.8	144.3±12.1	172.5±7.3	196.0±11.1	219.5±15.0	236.7±14.5

Notes: A2- A5: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B2-B5: 2, 3, 4 and 5ppm sodium selenite-treated groups; C2-C5: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls.

Table 4 The effects of Xiwang capsule, sodium selenite and selenoprotein on body weight of female rats

Groups	No. of rats	Week7	Week8	Week9	Week10	Week11	Week12	Week13
A2	12	240.0±14.4	248.8±16.2	265.2±20.6	266.7±15.2	276.2±20.9	284.2±19.3	281.3±25.0
A3	12	239.3±13.7	249.1±13.6	257.7±20.0	265.7±18.2	271.4±22.5	282.6±24.2	282.8±21.7
A4	12	228.3±17.5**	242.9±14.1*	251.8±18.8	255.8±19.2	263.6±20.2	269.5±19.6	271.3±20.4
A5	12	216.9±17.7**	227.7±21.6**	237.5±29.6**	246.4±36.7**	250.3±28.8*	250.1±30.1**	254.6±26.4**
B2	12	244.8±18.7	256.8±22.5	265.8±24.4	271.1±24.5	282.0±24.0	289.9±27.2	290.5±27.2
B3	12	217.4±18.6**	232.5±17.1**	242.3±17.4**	248.9±18.7*	256.5±20.9*	264.7±20.6*	260.9±21.5*
B4	12	218.6±20.1**	231.8±21.1**	234.5±20.2**	242.6±18.4**	246.1±18.1**	251.6±20.4**	256.0±20.3**
B5	12	203.3±14.1**	217.6±16.4**	230.0±20.0**	236.8±25.7**	241.8±25.7**	247.0±26.0**	248.8±24.1**
C2	12	248.3±17.5	261.1±22.0	277.1±35.1	275.6±18.7	274.1±20.7	286.1±22.7	288.6±22.1
C3	12	225.7±16.8**	237.6±19.3*	244.6±19.7*	252.5±25.6*	258.0±26.1*	261.9±26.0*	262.4±24.3*
C4	12	221.5±15.0**	232.5±17.8*	243.3±24.1*	250.3±25.7*	256.0±30.9*	258.8±30.2**	260.2±31.5*
C5	12	189.4±20.3**	194.7±23.6**	198.4±24.6**	209.4±24.2**	217.8±22.7**	228.0±19.4**	227.9±20.2**
Control	12	252.3±13.9	262.2±20.8	269.8±19.7	277.7±21.4	282.5±21.5	290.9±25.9	287.5±25.7

Notes: A2- A5: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B2-B5: 2, 3, 4 and 5ppm sodium selenite-treated groups; C2-C5: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls.

Table 5 The effects of Xiwang capsule, sodium selenite and selenoprotein on food efficiency

Groups	No. of rats	Male			Female		
		Total body weight gain (g)	Food consumption (g)	Food efficiency (%)	Total body weight gain (g)	Food consumption (g)	Food efficiency (%)
A2	12	442.8±49.4	1856.8±62.3	23.8±2.5	218.9±26.6	1517.5±170.3	14.6±2.1
A3	12	412.2±48.0	1858.3±148.3	22.3±3.1	220.3±22.2	1738.2±135.9	12.7±1.9
A4	12	414.3±42.7	1899.9±86.7	21.8±2.0	208.7±21.4	1703.2±184.3	12.4±1.9
A5	12	364.8±36.3**	1862.5±94.1	19.7±2.4**	192.0±28.4*	1441.4±182.2	13.7±3.4
B2	12	442.1±35.3	1867.4±65.7	23.7±1.8	227.8±25.9	1611.2±102.3	14.2±2.2
B3	12	431.5±36.4	1900.6±122.7	22.8±2.0	203.3±21.0	1678.1±144.9	12.2±1.7
B4	12	380.5±55.4**	1792.8±105.0	21.3±3.3*	193.9±20.9**	1536.3±118.0	12.7±1.5
B5	12	349.9±71.6**	1755.5±195.	19.9±3.7**	186.1±24.4**	1350.5±247.5	14.3±3.2
C2	12	438.3±49.8	1829.1±96.5	24.1±3.4	225.9±21.4	1663.7±131.4	13.6±1.4
C3	12	419.7±52.6	1914.3±177.5	22.0±3.1	199.6±22.2*	1555.9±185.6	13.0±1.8
C4	12	382.4±39.7**	1802.9±135.1	21.4±3.0	197.4±30.9*	1484.1±277.7	13.9±4.2
C5	12	335.3±57.2**	1535.6±176.8	22.1±4.6*	165.3±21.7**	1350.8±218.5	12.6±2.9
Control	12	448.3±55.4	1842.3±80.5	24.3±2.8	224.8±26.0	1599.2±135.1	14.3±2.6

Notes: A2- A5: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B2-B5: 2, 3, 4 and 5ppm sodium selenite-treated groups; C2-C5: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls.

Table 6 The effects of Xiwang capsule, sodium selenite and selenoprotein on hematology of males in the middle of the study

Groups	No. of rats	Red cell count ($\times 10^{12}/L$)	Hemoglobin (g/L)	Platelet count ($\times 10^9/L$)	White cell count ($\times 10^{12}/L$)	White cell differential count		
						Lymphocyte (%)	Neutrophil (%)	Other cells (%)
A2	12	7.99 \pm 0.64	139.1 \pm 10.2	657.9 \pm 207.4	22.1 \pm 6.09	71.8 \pm 4.73	21.3 \pm 4.47	6.87 \pm 1.47
A3	12	8.32 \pm 0.96	141.7 \pm 15.1	551.5 \pm 395.9	21.1 \pm 7.58	69.2 \pm 5.38	24.3 \pm 4.97	6.45 \pm 0.98
A4	12	8.23 \pm 0.60	145.0 \pm 9.3	440.9 \pm 86.39	25.9 \pm 5.69	69.1 \pm 5.15	23.7 \pm 4.01	7.19 \pm 1.94
A5	12	6.94 \pm 1.24*	125.3 \pm 22.6*	312.3 \pm 126.3	27.7 \pm 6.57	70.5 \pm 2.24	22.5 \pm 2.00	6.97 \pm 1.20
B2	12	7.81 \pm 0.55	141.9 \pm 8.2	430.3 \pm 82.3	27.1 \pm 6.16	73.8 \pm 3.37	19.8 \pm 2.76	6.33 \pm 1.28
B3	12	7.81 \pm 0.57	138.2 \pm 5.4	409.6 \pm 91.8	23.0 \pm 4.69	72.2 \pm 4.12	20.6 \pm 3.92	7.17 \pm 1.18
B4	12	7.43 \pm 1.04	131.9 \pm 16.3	413.7 \pm 106.8	24.0 \pm 4.57	71.8 \pm 2.66	21.2 \pm 2.60	6.93 \pm 1.11
B5	12	6.96 \pm 0.81*	122.5 \pm 14.2**	277.1 \pm 120.5**	24.9 \pm 6.90	71.3 \pm 3.87	20.7 \pm 3.84	7.94 \pm 1.38
C2	12	8.14 \pm 0.39	144.0 \pm 10.5	452.5 \pm 119.0	18.5 \pm 5.35	71.3 \pm 4.86	21.2 \pm 4.29	7.36 \pm 1.53
C3	12	7.92 \pm 0.51	137.6 \pm 9.0	416.9 \pm 78.2	18.9 \pm 6.44	73.8 \pm 5.99	19.5 \pm 5.73	6.67 \pm 1.70
C4	12	7.57 \pm 0.51	134.3 \pm 6.7	374.6 \pm 94.4	25.3 \pm 5.48	71.3 \pm 5.62	21.1 \pm 4.10	7.63 \pm 2.13
C5	12	5.91 \pm 1.9**	105.8 \pm 33.3**	281.1 \pm 162.8**	27.5 \pm 5.00	66.7 \pm 3.18	24.5 \pm 3.28	8.74 \pm 1.37
Control	12	7.97 \pm 0.68	142.1 \pm 14.6	465.9 \pm 74.5	23.7 \pm 6.12	70.7 \pm 5.05	22.4 \pm 4.44	6.84 \pm 1.31

Notes: A2- A5: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B2-B5: 2, 3, 4 and 5ppm sodium selenite-treated groups; C2-C5: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls.

Table 7 The effects of Xiwang capsule, sodium selenite and selenoprotein on hematology of females in the middle of the study

Groups	No. of rats	Red cell count ($\times 10^{12}/L$)	Hemoglobin (g/L)	Platelet count ($\times 10^9/L$)	White cell count ($\times 10^{12}/L$)	White cell differential count		
						Lymphocyte (%)	Neutrophil (%)	Other cells (%)
A2	12	7.45 \pm 1.20	136.5 \pm 20.3	446.0 \pm 72.9	23.1 \pm 7.88	72.5 \pm 4.13	21.02 \pm 3.34	6.50 \pm 1.01
A3	12	7.68 \pm 0.45	139.0 \pm 9.95	393.4 \pm 64.3	22.5 \pm 7.17	66.0 \pm 5.35	26.3 \pm 5.20	6.60 \pm 0.99
A4	12	8.17 \pm 0.44	139.8 \pm 7.91	423.4 \pm 85.9	23.2 \pm 6.84	65.5 \pm 10.2	26.7 \pm 8.91	7.72 \pm 1.49
A5	12	7.99 \pm 0.45	138.6 \pm 10.0	346.9 \pm 78.3	23.8 \pm 6.98	69.9 \pm 7.97	23.4 \pm 8.23	6.71 \pm 0.90
B2	12	8.09 \pm 0.78	143.1 \pm 12.5	373.7 \pm 87.0	21.9 \pm 8.49	71.3 \pm 6.43	21.53 \pm 6.23	7.18 \pm 1.10
B3	12	8.45 \pm 0.73	144.8 \pm 19.1	331.8 \pm 41.4	23.2 \pm 6.46	69.9 \pm 3.87	22.9 \pm 3.89	7.17 \pm 0.90
B4	12	7.71 \pm 0.77	136.9 \pm 15.0	325.6 \pm 100.2	21.1 \pm 5.23	72.3 \pm 3.51	20.0 \pm 3.08	7.66 \pm 1.10
B5	12	7.23 \pm 0.69*	132.1 \pm 14.3*	264.9 \pm 81.9*	23.9 \pm 6.14	72.8 \pm 5.61	19.9 \pm 5.50	7.31 \pm 0.93
C2	12	7.71 \pm 0.73	140.3 \pm 11.6	428.2 \pm 97.3	18.8 \pm 4.64	72.4 \pm 4.94	21.2 \pm 4.02	6.35 \pm 1.37
C3	12	7.82 \pm 0.75	125.1 \pm 13.1	360.8 \pm 140.4	21.2 \pm 7.11	70.7 \pm 5.67	22.6 \pm 4.52	6.69 \pm 1.65
C4	12	7.07 \pm 1.10**	125.2 \pm 17.2**	293.4 \pm 127.9	20.4 \pm 8.13	72.9 \pm 4.27	19.7 \pm 3.62	7.38 \pm 1.77
C5	12	6.85 \pm 0.69**	120.5 \pm 11.7**	193.2 \pm 129.2**	19.7 \pm 7.85	68.4 \pm 5.68	22.9 \pm 5.45	7.61 \pm 1.22
Control	12	8.08 \pm 0.45	149.5 \pm 5.45	402.7 \pm 76.8	19.1 \pm 3.71	72.4 \pm 3.76	21.2 \pm 3.05	6.37 \pm 0.92

Notes: A2- A5: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B2-B5: 2, 3, 4 and 5ppm sodium selenite-treated groups; C2-C5: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls.

Table 8 The effects of Xiwang capsule, sodium selenite and selenoprotein on hematology of males at the end of the study

Groups	No. of rats	Red cell count ($\times 10^{12}/L$)	Hemoglobin (g/L)	Platelet count ($\times 10^9/L$)	White cell count ($\times 10^{12}/L$)	White cell differential count		
						Lymphocyte (%)	Neutrophil (%)	Other cells (%)
A2	12	8.54 \pm 0.47	152.6 \pm 6.61	487.7 \pm 157.0	25.5 \pm 9.03	78.2 \pm 3.78	14.9 \pm 3.69	6.85 \pm 0.91
A3	12	7.94 \pm 0.62	151.3 \pm 9.83	458.9 \pm 128.7	22.3 \pm 6.73	75.1 \pm 5.08	17.7 \pm 4.96	7.10 \pm 0.62
A4	12	8.23 \pm 0.60	151.3 \pm 10.9	425.9 \pm 120.1	24.1 \pm 5.43	73.4 \pm 4.28	19.3 \pm 4.00	7.23 \pm 1.03
A5	12	7.71 \pm 0.48*	139.1 \pm 12.0*	416.8 \pm 167.6	22.0 \pm 7.10	73.5 \pm 4.61	19.0 \pm 4.31	7.34 \pm 1.00
B2	12	7.90 \pm 0.65	151.9 \pm 7.17	536.1 \pm 85.6	22.9 \pm 5.94	75.2 \pm 7.49	17.4 \pm 6.54	7.35 \pm 1.34
B3	12	7.58 \pm 0.71	142.6 \pm 14.1	427.3 \pm 155.0	21.6 \pm 4.71	79.3 \pm 4.41	14.1 \pm 4.31	6.53 \pm 1.01
B4	12	7.37 \pm 0.69*	144.0 \pm 13.2	381.1 \pm 86.04*	24.3 \pm 8.21	73.0 \pm 7.67	19.2 \pm 6.87	7.78 \pm 1.39
B5	12	7.36 \pm 1.23*	134.0 \pm 21.6*	406.0 \pm 151.8*	21.0 \pm 10.7	74.6 \pm 7.45	17.6 \pm 7.06	7.70 \pm 1.30
C2	12	7.97 \pm 0.55	154.1 \pm 7.94	477.0 \pm 112.1	22.0 \pm 10.4	77.9 \pm 5.06	15.1 \pm 4.36	6.87 \pm 1.30
C3	12	7.51 \pm 1.00	146.3 \pm 19.8	412.5 \pm 129.1	18.1 \pm 7.09	77.0 \pm 3.13	16.3 \pm 3.15	6.68 \pm 1.22
C4	12	8.05 \pm 0.85	151.3 \pm 14.8	434.0 \pm 108.2	27.4 \pm 6.31	75.1 \pm 3.50	17.2 \pm 4.70	7.63 \pm 2.80
C5	12	7.05 \pm 0.91**	139.3 \pm 13.8*	438.1 \pm 137.2	23.2 \pm 8.61	70.8 \pm 7.61	21.4 \pm 6.57	7.76 \pm 1.26
Control	12	8.34 \pm 0.65	157.4 \pm 9.69	527.9 \pm 103.2	19.1 \pm 6.90	74.8 \pm 4.07	17.5 \pm 4.28	7.65 \pm 1.01

Notes: A2- A5: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B2-B5: 2, 3, 4 and 5ppm sodium selenite-treated groups; C2-C5: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls.

Table 9 The effects of Xiwang capsule, sodium selenite and selenoprotein on hematology of females at the end of the study

Groups	No. of rats	Red cell count ($\times 10^{12}/L$)	Hemoglobin (g/L)	Platelet count ($\times 10^9/L$)	White cell count ($\times 10^{12}/L$)	White cell differential count		
						Lymphocyte (%)	Neutrophil (%)	Other cells (%)
A2	12	7.28 \pm 0.53	150.3 \pm 12.1	438.1 \pm 98.3	20.7 \pm 11.3	80.3 \pm 7.04	12.3 \pm 6.26	7.27 \pm 0.99
A3	12	7.62 \pm 1.21	146.3 \pm 24.6	449.4 \pm 120.0	16.2 \pm 5.55	77.6 \pm 7.79	14.9 \pm 6.44	7.47 \pm 1.97
A4	12	7.33 \pm 0.38	146.9 \pm 6.42	441.4 \pm 150.3	18.4 \pm 6.17	79.7 \pm 4.68	13.3 \pm 4.24	6.90 \pm 0.85
A5	12	7.41 \pm 0.50	144.7 \pm 9.05	438.1 \pm 139.8	19.7 \pm 7.92	77.8 \pm 7.27	15.5 \pm 8.22	6.68 \pm 1.31
B2	12	7.17 \pm 0.63	146.1 \pm 12.0	428.7 \pm 96.0	19.6 \pm 6.87	81.2 \pm 4.73	11.9 \pm 4.60	6.74 \pm 1.18
B3	12	7.16 \pm 0.60	144.4 \pm 8.84	412.5 \pm 126.7	23.3 \pm 14.0	75.7 \pm 12.5	17.0 \pm 11.5	7.19 \pm 1.69
B4	12	6.68 \pm 0.69	139.3 \pm 11.5**	345.5 \pm 70.9*	22.1 \pm 5.61	75.9 \pm 7.68	16.9 \pm 6.52	7.08 \pm 1.53
B5	12	6.62 \pm 0.62**	137.1 \pm 13.8**	357.1 \pm 58.3*	21.3 \pm 7.22	81.7 \pm 7.02	12.0 \pm 6.66	6.24 \pm 0.82
C2	12	6.97 \pm 0.65	145.0 \pm 11.6	455.6 \pm 94.0	16.1 \pm 5.59	80.3 \pm 4.61	12.6 \pm 4.85	7.02 \pm 1.24
C3	12	7.29 \pm 0.96	148.2 \pm 19.0	372.9 \pm 138.6	19.7 \pm 11.6	82.0 \pm 4.80	11.1 \pm 4.59	6.87 \pm 0.80
C4	12	6.99 \pm 0.41	139.4 \pm 8.03**	391.9 \pm 119.3	22.8 \pm 7.90	76.1 \pm 5.81	16.0 \pm 4.74	7.81 \pm 2.04
C5	12	6.26 \pm 0.67**	128.5 \pm 9.01**	359.9 \pm 124.0	21.5 \pm 9.70	75.7 \pm 3.45	16.9 \pm 3.98	7.32 \pm 1.41
Control	12	7.50 \pm 0.54	154.8 \pm 10.0	463.6 \pm 55.8	16.4 \pm 4.37	82.5 \pm 5.83	11.5 \pm 5.37	5.96 \pm 1.07

Notes: A2- A5: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B2-B5: 2, 3, 4 and 5ppm sodium selenite-treated groups; C2-C5: 2, 3, 4 and 5ppm selenoprotein-treated groups * $p < 0.05$, as compared with the controls; ** $p < 0.01$, as compared with the controls.

Table 10 The effects of Xiwang capsule, sodium selenite and selenoprotein on clinical chemistry of males in the middle of the study

Groups	No. of rats	ALT (U/L)	AST (U/L)	BUN (mmol/L)	TC (mmol/L)	CRE (umol/L)	TG (mmol/L)	GLU (mmol/L)	TP (g/L)	ALB (g/L)
A2	12	58.8±15.7	193.8±34.5	5.39±0.93	1.55±0.15	66.4±4.75	1.15±0.63	5.39±0.73	70.8±5.91	35.7±1.59
A3	12	52.3±10.7	200.5±42.3	5.20±0.73	1.70±0.19	67.4±5.93	1.44±0.43	5.35±0.54	73.2±2.81	36.4±1.02
A4	12	60.1±14.1	224.0±41.0	5.98±1.35	1.73±0.22	65.1±4.62	0.90±0.40	5.29±0.66	70.6±4.56	35.8±1.51
A5	12	62.7±12.7	200.8±31.9	5.08±0.65	1.67±0.32	61.1±11.59	0.80±0.27	5.73±0.58	63.1±9.64	33.3±4.03
B2	12	46.8±17.5	198.3±47.4	5.28±1.04	1.73±0.26	61.6±16.7	1.16±0.65	5.68±0.49	68.0±4.17	35.2±1.10
B3	12	51.2±8.5	205.9±47.8	5.65±1.10	1.79±0.22	62.9±2.82	1.19±0.39	5.68±0.57	66.9±2.86	35.3±0.70
B4	12	71.8±30.7	216.5±35.1	5.59±0.93	1.87±0.30	66.1±5.28	0.94±0.35	5.56±0.54	68.8±3.04	35.1±1.50
B5	12	85.3±29.7**	205.3±27.1	5.03±0.99	1.97±0.37	61.4±5.14	0.58±0.24	5.46±0.55	62.9±5.91	32.9±2.51**
C2	12	52.2±7.7	223.8±36.0	5.22±0.73	1.61±0.25	64.8±5.56	1.35±0.40	5.26±0.51	67.9±4.72	35.4±1.42
C3	12	58.7±13.1	229.9±52.2	5.76±0.84	1.76±0.22	63.5±5.53	1.18±0.56	5.58±0.69	70.4±5.68	35.2±1.89
C4	12	61.4±21.2	217.4±47.4	5.53±0.89	1.76±0.37	63.2±20.70	0.92±0.35	5.24±0.93	68.1±5.19	34.78±1.60
C5	12	116.6±56.2**	279.2±140.2*	6.48±6.35	2.06±1.01	62.6±16.23	0.81±0.94	5.19±0.71	58.3±12.68**	30.8±5.53**
Control	12	53.0±4.6	208.8±42.6	5.75±1.53	1.80±0.20	69.8±12.11	1.311±0.71	5.49±0.53	68.7±4.68	35.3±1.54

Notes: A2- A5: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B2-B5: 2, 3, 4 and 5ppm sodium selenite-treated groups; C2-C5: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, albumin; GLU, glucose; BUN, urea nitrogen; CRE, creatinine; TC, total cholesterol; and TG, triglyceride.

Table 11 The effects of Xiwang capsule, sodium selenite and selenoprotein on clinical chemistry of females in the middle of the study

Groups	No. of rats	ALT (U/L)	AST (U/L)	BUN (mmol/L)	TC (mmol/L)	CRE (umol/L)	TG (mmol/L)	GLU (mmol/L)	TP (g/L)	ALB (g/L)
A2	12	50.8±10.8	157.7±22.9	6.02±0.49	1.94±0.24	68.7±6.42	1.08±0.45	6.01±0.23	71.5±6.11	36.3±2.45
A3	12	51.6±12.0	158.9±27.7	5.83±0.48	2.25±0.31	69.1±3.15	1.09±0.41	6.01±0.48	73.6±3.63	36.7±1.23
A4	12	49.0±17.6	141.2±53.2	5.57±0.80	1.95±0.52	64.0±14.89	0.86±0.25	6.19±0.44	71.3±5.52	36.4±1.13
A5	12	62.9±18.9**	154.2±27.7	5.82±1.43	2.04±0.42	66.7±4.44	0.75±0.30	6.51±0.83	64.6±6.12**	34.2±2.60**
B2	12	48.3±9.6	127.6±21.6	6.12±0.54	2.23±0.29	72.6±5.43	1.47±0.35	6.43±0.80	74.3±5.67	38.06±1.78
B3	12	56.8±16.3	151.2±32.3	7.52±2.13	2.16±0.20	82.5±19.18	0.98±0.31	6.29±0.51	70.1±4.56	36.3±1.34
B4	12	62.6±12.5*	146.5±18.6	6.48±1.11	2.13±0.37	71.5±7.83	0.65±0.15	6.67±0.48	69.3±5.69	35.9±5.17
B5	12	71.0±23.2**	148.7±32.9	6.28±1.46	1.91±0.34	66.0±8.41	0.62±0.23	6.75±0.33	63.5±9.01**	34.1±3.36**
C2	12	47.7±7.5	145.1±35.1	5.81±0.75	2.13±0.33	67.8±13.82	1.06±0.38	6.54±0.36	71.3±3.40	36.9±1.03
C3	12	63.2±12.6	180.7±61.0	5.13±1.41	2.00±0.37	69.9±8.02	0.75±0.29	6.29±0.45	68.5±3.90	35.3±1.88*
C4	12	73.4±20.2**	163.2±31.6	5.76±1.64	1.95±0.26	69.1±17.77	0.87±0.18	6.02±0.89	65.7±7.96**	34.3±2.92*
C5	12	91.9±38.3**	160.8±50.3	5.64±0.51	1.89±0.26	67.0±8.98	0.78±0.18	6.11±0.33	57.7±8.31**	31.4±3.70**
Control	12	46.2±6.8	137.3±23.7	6.15±0.89	1.93±0.17	71.8±4.67	0.97±0.47	6.48±0.51	73.4±3.94	38.1±1.28

Notes: A2- A5: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B2-B5: 2, 3, 4 and 5ppm sodium selenite-treated groups; C2-C5: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, albumin; GLU, glucose; BUN, urea nitrogen; CRE, creatinine; TC, total cholesterol; and TG, triglyceride.

Table 12 The effects of Xiwang capsule, sodium selenite and selenoprotein on clinical chemistry of males at the end of the study

Groups	No. of rats	ALT (U/L)	AST (U/L)	BUN (mmol/L)	TC (mmol/L)	CRE (umol/L)	TG (mmol/L)	GLU (mmol/L)	TP (g/L)	ALB (g/L)
A2	12	58.3±22.1	194.2±76.7	6.21±0.98	1.83±0.30	76.4±8.43	1.27±0.10	5.64±0.44	75.87±6.08	33.2±1.45
A3	12	57.7±35.1	173.0±35.1	5.76±0.24	1.89±0.28	72.9±6.34	1.23±0.77	5.32±0.29	72.9±5.48	34.4±2.07
A4	12	60.1±10.9	189.2±30.5	5.93±0.56	1.64±0.25	72.4±6.66	1.34±0.25	5.37±0.33	70.1±5.39	33.4±1.35
A5	12	68.8±18.6*	151.7±17.4	5.69±0.59	1.87±0.22	67.9±4.25	1.07±0.40	5.14±0.39	70.9±3.76	32.6±1.15
B2	12	60.0±16.6	154.6±35.2	6.50±0.98	1.82±0.51	72.9±6.71	1.26±0.80	5.16±0.68	74.8±5.80	33.0±1.79
B3	12	52.6±9.30	157.4±35.9	6.05±1.01	1.98±0.38	74.8±4.79	1.34±0.64	5.71±0.74	76.6±3.13	33.8±0.73
B4	12	66.3±15.2*	177.0±38.4	6.12±0.55	1.82±0.30	71.6±9.43	1.15±0.57	5.66±0.62	73.7±7.11	33.0±2.07
B5	12	69.3±22.3**	187.2±52.0	6.53±0.69	1.97±0.43	71.0±5.68	1.17±0.49	5.27±0.41	70.5±5.44	31.8±1.99
C2	12	67.9±29.0	174.6±32.0	5.61±0.46	1.85±0.46	72.7±6.15	1.65±0.35	5.47±0.53	76.0±3.50	33.2±1.11
C3	12	66.3±17.6	175.3±39.1	6.11±0.78	1.86±0.24	74.5±4.64	1.23±0.89	5.46±0.67	75.7±4.54	33.5±1.44
C4	12	63.6±25.8	164.8±43.5	6.12±0.75	1.97±0.35	72.0±6.09	1.46±0.77	5.35±0.63	71.5±4.89	33.5±1.42
C5	12	74.7±21.6*	201.1±39.5*	6.12±1.13	1.77±0.45	68.5±5.03	0.99±0.51	5.03±0.78	70.4±5.33	32.0±1.29
Control	12	49.0±6.90	167.8±45.3	5.96±1.05	1.65±0.27	73.6±6.41	1.12±0.45	4.95±1.01	72.5±3.96	33.0±1.32

Notes: A 2- A 5: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B2-B5: 2, 3, 4 and 5ppm sodium selenite-treated groups; C2-C5: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, albumin; GLU, glucose; BUN, urea nitrogen; CRE, creatinine; TC, total cholesterol; and TG, triglyceride.

Table 13 The effects of Xiwang capsule, sodium selenite and selenoprotein on clinical chemistry of females at the end of the study

Groups	No. of rats	ALT (U/L)	AST (U/L)	BUN (mmol/L)	TC (mmol/L)	CRE (umol/L)	TG (mmol/L)	GLU (mmol/L)	TP (g/L)	ALB (g/L)
A2	12	58.7±16.2	179.7±43.1	6.68±1.03	2.49±0.51	78.64±9.14	127±0.68	5.53±0.98	80.80±8.45	35.2±3.19
A3	12	53.8±15.7	183.8±61.2	6.82±1.09	2.21±0.22	77.03±9.82	1.39±1.13	5.13±0.81	77.74±6.89	34.9±2.75
A4	12	64.1±14.5	174.2±28.3	7.41±1.32	2.37±0.41	80.5±7.36	1.18±0.35	5.27±0.71	84.6±9.86	36.2±1.18
A5	12	84.3±23.7*	195.3±51.9	6.91±1.53	2.15±0.31	78.0±3.88	0.70±0.32	5.20±0.44	76.2±7.56	34.43±2.25
B2	12	60.6±15.1	170.3±50.9	6.43±1.17	2.34±0.35	77.8±6.21	1.82±0.71	5.19±0.66	84.5±3.35	36.8±1.25
B3	12	67.1±22.3	155.8±35.2	5.77±0.39	2.36±0.33	77.4±7.36	1.21±0.45	6.06±0.36	79.1±6.85	34.9±2.17
B4	12	67.8±18.7	158.5±40.0	6.55±1.21	2.10±0.41	77.5±4.01	0.82±0.32	5.28±0.55	75.2±5.18*	33.1±1.52**
B5	12	91.8±45.4**	184.0±55.9	5.07±0.61	2.54±0.65	67.0±5.29	0.88±0.31	5.47±0.53	68.9±6.75**	31.4±2.80**
C2	12	56.3±11.3	142.8±40.2	7.32±1.07	2.23±0.35	80.4±5.70	1.50±0.62	6.03±0.42	82.0±5.76	38.1±3.59
C3	12	62.3±21.9	157.3±34.6	7.29±1.22	2.41±0.42	77.4±5.40	0.97±0.19	5.77±0.53	78.2±4.59	34.5±1.64
C4	12	76.0±23.7**	169.3±24.3	6.52±1.03	2.35±0.58	74.1±8.72	1.10±0.24	5.81±0.47	76.9±8.41	34.0±2.86
C5	12	86.6±23.4*	189.5±64.0**	5.88±0.83	1.91±0.59	69.7±7.29	1.08±0.24	5.73±0.27	71.7±6.59**	31.73±2.84**
Control	12	48.2±14.3	142.0±20.1	5.94±0.96	2.16±0.43	78.7±6.37	1.34±0.68	5.72±0.75	81.0±4.06	36.6±1.72

Notes: A 2- A 5: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B2-B5: 2, 3, 4 and 5ppm sodium selenite-treated groups; C2-C5: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, albumin; GLU, glucose; BUN, urea nitrogen; CRE, creatinine; TC, total cholesterol; and TG, triglyceride.

Table 14 The effects of Xiwang capsule, sodium selenite and selenoprotein on the relative weight of males

Groups	No. of rats	Relative liver weight (%)	Relative kidney weight (%)	Relative spleen weight (%)	Relative testis/ovary weight (%)	Relative brain weight (%)	Relative heart weight (%)
A ₂	12	2.49±0.18	0.64±0.07	0.21±0.06	0.73±0.12	0.47±0.06	0.30±0.03
A ₃	12	2.32±0.32	0.61±0.18	0.19±0.04	0.75±0.08	0.46±0.04	0.30±0.03
A ₄	12	2.54±0.46	0.66±0.05	0.18±0.03	0.73±0.09	0.45±0.04	0.30±0.03
A ₅	12	2.76±0.33**	0.69±0.03	0.29±0.09**	0.80±0.10	0.54±0.05**	0.35±0.07**
B ₂	12	2.55±0.33	0.62±0.11	0.18±0.03	0.64±0.16	0.43±0.06	0.27±0.05
B ₃	12	2.60±0.24	0.64±0.07	0.18±0.02	0.69±0.06	0.43±0.04	0.26±0.03
B ₄	12	2.90±0.66**	0.70±0.11	0.22±0.05*	0.78±0.08	0.50±0.05	0.33±0.03**
B ₅	12	2.95±0.62**	0.64±0.08	0.33±0.07**	0.72±0.12	0.49±0.05**	0.32±0.04*
C ₂	12	2.59±0.38	0.68±0.08	0.18±0.03	0.75±0.09	0.46±0.05*	0.28±0.07
C ₃	12	2.47±0.24	0.66±0.06	0.17±0.01	0.78±0.11	0.46±0.05	0.30±0.03
C ₄	12	2.85±0.25**	0.75±0.09**	0.19±0.03	0.82±0.12**	0.50±0.07*	0.32±0.03
C ₅	12	2.93±0.56**	0.74±0.10**	0.29±0.09**	0.86±0.11**	0.58±0.08**	0.36±0.06**
Control	12	2.30±0.43	0.63±0.06	0.17±0.02	0.69±0.09	0.44±0.04	0.28±0.02

Notes: A₂- A₅: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B₂-B₅: 2, 3, 4 and 5ppm sodium selenite-treated groups; C₂-C₅: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls.

Table 15 The effects of Xiwang capsule, sodium selenite and selenoprotein on the relative weight of females

Groups	No. of rats	Relative liver weight (%)	Relative kidney weight (%)	Relative spleen weight (%)	Relative testis/ovary weight (%)	Relative brain weight (%)
A ₂	12	2.48±0.28	0.62±0.06	0.19±0.03	0.64±0.05	0.28±0.02
A ₃	12	2.44±0.51	0.63±0.08	0.22±0.06	0.65±0.08	0.28±0.10
A ₄	12	2.59±0.42	0.62±0.11	0.22±0.02	0.69±0.10	0.30±0.04
A ₅	12	2.88±0.35**	0.67±0.08	0.32±0.08**	0.72±0.06	0.34±0.04**
B ₂	12	2.54±0.26	0.64±0.05	0.22±0.03	0.60±0.12	0.30±0.03
B ₃	12	2.80±0.26	0.60±0.04	0.24±0.04	0.70±0.07	0.30±0.03
B ₄	12	2.92±0.43*	0.64±0.11	0.27±0.05*	0.72±0.10	0.32±0.04
B ₅	12	3.08±1.32**	0.70±0.11**	0.45±0.14**	0.70±0.15	0.42±0.11**
C ₂	12	2.42±0.15	0.62±0.06	0.20±0.04	0.65±0.05	0.31±0.05
C ₃	12	2.71±0.19**	0.65±0.07	0.22±0.02	0.71±0.06	0.32±0.02
C ₄	12	2.70±0.27**	0.65±0.05	0.24±0.05	0.73±0.07**	0.32±0.03
C ₅	12	2.65±0.58**	0.71±0.10**	0.42±0.10**	0.77±0.07**	0.36±0.04**
Control	12	2.21±0.25	0.59±0.05	0.19±0.03	0.65±0.07	0.28±0.03

Notes: A₂- A₅: 2, 3, 4 and 5ppm Xiwang capsule-treated groups; B₂-B₅: 2, 3, 4 and 5ppm sodium selenite-treated groups; C₂-C₅: 2, 3, 4 and 5ppm selenoprotein-treated groups * p<0.05, as compared with the controls; ** p<0.01, as compared with the controls.

Tabel 16 Gross examination results of rats in Xiwang capsule, sodium selenite and selenoprotein-treated groups

Sex	Groups	No. of rats	2ppm		3 ppm		4 ppm			5 ppm	
			Normal	Abnormal	Normal	Abnormal	Normal	Rough surface	Hepatic nodules	Rough Surface	Hepatic nodules
Male	Xiwang capsule	12	12	0	12	0	7	5	0	6	6 (50%) ^b
	Sodium selenite	12	12	0	12	0	5	7	0	4	8 (66.6%)
	Selenoprotein	12	12	0	12	0	3	9	0	0	12 (100%)
	Control	12	12	0							
Female	Xiwang capsule	12	12	0	12	0	8	4	0 ^a	5	7 (58.3%) ^a
	Sodium selenite	12	12	0	12	0	0	8	4	0	12 (100%)
	Selenoprotein	12	12	0	12	0	2	9	1	0	12 (100%)
	Control	12	12	0							

a: $p < 0.05$, as compared with sodium selenite and selenoprotein

b: $p < 0.05$, as compared with selenoprotein

Table 17 Histopathological examination results of rats in Xiwang capsule, sodium selenite and selenoprotein-treated groups

Sex	Groups	No. of rats	2ppm		3 ppm		4 ppm			5 ppm		
			Normal	Abnormal	Normal	Structure disturbance	Normal	Structure disturbance	Structure damage	Normal	Structure disturbance	Structure damage
Male	Xiwang capsule	12	12	0	12	0	4	5 ^c	3 ^c	0	8	4
	Sodium selenite	12	12	0	9	3	0	6	6	0	1	11
	Selenoprotein	12	12	0	9	3	0	9	3	0	0	12
	Control	12	12									
Female	Xiwang capsule	12	12	0	12	0 ^d	2	7	3 ^b	0	9	3 ^a
	Sodium selenite	12	12	0	7	5	0	4	8	0	3	9
	Selenoprotein	12	12	0	9	3	0	1	11	0	2	10
	Control	12	12									

a and b: p<0.05, incidence of structure damage, compared with sodium selenite and selenoprotein group

c: p<0.05, incidence of structure disturbance and damage, compared with sodium selenite and selenoprotein group

d: p<0.05, incidence of structure disturbance, compared with sodium selenite group

Table 18 A summary of the 90-day feeding test of Xiwang capsule, sodium selenite and selenoprotein

Sex	Group	Growth			Hematology			Clinical chemistry			Relative organ weight			Histopathology		
		NOAEL (ppm)	LOAEL (ppm)	Effective end point	NOAEL (ppm)	LOAEL (ppm)	Effective end point	NOAEL (ppm)	LOAEL (ppm)	Effective end point	NOAEL (ppm)	LOAEL (ppm)	Effective end point	NOAEL (ppm)	LOAEL (ppm)	Effective end point
Male	Xiwang capsule	4	5	Body weight	4	5	RBC, Hb	4	5	AST, TP, ALB	4	5	Liver, spleen, brain, heart	3	4	liver
	Sodium selenite	3	4	Body weight	3	4	RBC, PLT	3	4	AST	3	4	Liver, spleen, heart	2	3	liver
	Seleno-protein	3	4	Body weight	4	5	RBC, Hb, PLT	4	5	AST, ALT, TP, ALB	3	4	Liver, kidney, brain, testis	2	3	liver
Female	Xiwang capsule	4	5	Body weight	5	Not observed	RBC, Hb, PLT, WBC	4	5	AST, TP, ALB	4	5	Liver, spleen, heart	3	4	liver
	Sodium selenite	2	3	Body weight	3	4	Hb, PLT	3	4	AST, TP, ALB	3	4	Liver, spleen,	2	3	liver
	Seleno-protein	2	3	Body weight	3	4	RBC, Hb,	3	4	AST, TP, ALB	2	3	Liver	2	3	liver

Notes: NOAEL, non-observed-adverse-effect-level; LOAEL, least-observed-adverse-effect-level; HB, hemoglobin; RBC, red cell count; WBC, total white cell count; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, albumin; GLU, glucose; BUN, urea nitrogen; C, creatinine; T-Chol, total cholesterol; TG, triglyceride

