EVALUATION OF ACUTE AND SUBCHRONIC ORAL TOXICITY OF S-MEN IN EXPERIMENTAL *WISTAR* RATS

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This study aimed to assess the acute and repeated-dose oral toxicity of the S-Men formulation in experimental animals. Acute toxicity was evaluated in Wistar rats via oral administration following the OECD 423 fixed-dose method. Subchronic toxicity was investigated through a 90-day repeated-dose oral study per OECD 408 guidelines. The acute toxicity results demonstrated that S-Men at doses up to 5000 mg/kg did not cause acute toxicity, and the LD_{50} could not be determined. In the repeated-dose study, S-Men administered at 1096 mg/kg/day and 3288 mg/kg/day for 90 consecutive days caused no significant change in general condition, body weight, hematological and biochemical parameters, or liver and kidney histopathology compared to the normal control group. Thus, S-Men exhibited no acute toxicity at doses up to 5000 mg/kg and did not cause subchronic toxicity at 1096 and 3288 mg/kg/day over 12 weeks in Wistar rats.

Keywords: S-Men, acute toxicity, repeated-dose toxicity, *Wistar* rats.

I. INTRODUCTION

Male infertility is an increasingly prevalent public health issue, particularly in developing countries, with rising rates linked to lifestyle factors and associated comorbidities. In Vietnam, studies have reported a high prevalence of erectile dysfunction among married men, influenced by multiple factors.[1] A central mechanism in male infertility is oxidative stress, which damages sperm DNA, impairs motility, and reduces fertilization capacity.[2] Recent research supports the efficacy of antioxidant supplementation and compounds that enhance reproductive function.[3,4]

S-Men is a composite formulation containing myo-inositol, L-carnitine, L-arginine, vitamin E, zinc, and selenium, each backed by scientific evidence for improving semen quality and protecting sperm from oxidative stress. Myo-inositol enhances sperm parameters such as count, viability, morphology, and motility in diabetic rats by reducing oxidative stress and regulating apoptosis-related genes.[3] L-carnitine improves sperm quality and reproductive hormone expression in *Wistar* rat models,[4] while vitamin E, zinc, and selenium serve as critical antioxidants, safeguarding sperm cell membranes.[5]

Although individual components of S-Men have been reported to possess favorable safety profiles, comprehensive data regarding the acute and repeated-dose toxicity of the combined formulation remain limited. The co-administration of multiple bioactive compounds may lead to potential toxicological interactions, particularly with repeated or long-term use. According to international regulatory guidelines, including OECD Test Guidelines 423 and 408, evaluation of acute and subchronic oral toxicity in experimental animals is required to establish the safety of multi-component formulations prior to widespread clinical application.[6,7] This study systematically investigates the acute and

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subchronic oral toxicity of S-Men in *Wistar* rats, providing foundational safety data to support its clinical development.

II. MATERIALS AND METHODS

1. Study materials

Investigational product

S-Men contains the following active ingredients: 1.000 mg of Myo-inositol, 1.000 mg of L-Carnitine, 100 mg of L-Arginine, 20 mg of Vitamin E (DL-α-tocopheryl acetate), 5 mg of Zinc (zinc citrate), 50 µg of Selenium (sodium selenite), and other excipients q.s. per sachet.

S-Men is manufactured by Fortex Nutraceuticals Ltd. (Bulgaria) and distributed in Vietnam by MID Pharmaceutical Joint Stock Company under registration number 3357/2019/ĐKSP. The product is formulated as a powder for oral administration. The recommended dosage is one sachet per day, dissolved in 250 mL of water, taken 30 minutes before meals.

Experimental animals

Adult *Wistar* rats (both sexes, 170–250 g) were used for the repeated-dose toxicity study. Animals were housed in a controlled laboratory environment at 25 ± 1°C, with appropriate humidity and lighting, at the Department of Pharmacology, Hanoi Medical University. Rats were acclimatized for 7 days before the study and had access to standard rodent chow and water *ad libitum* throughout the experiment.

2. Study methods

Acute oral toxicity assessment

The acute toxicity of S-Men was evaluated in accordance with OECD Guideline 423 (Acute Toxic Class Method).[6] The test product was suspended in water and administered to rats as a single oral dose after 24 hours of fasting. Rats were divided into six groups, each consisting of three animals: a control group and groups receiving doses of 5, 50, 300, 2000, and 5000 mg/kg body weight. The control group received only water to assess the vehicle's effect. After administration of the test product at a dose of 5000 mg/kg with an administration volume of 1 mL/100 g body weight, the animals were observed for 24 hours, with particular attention during the first 4 hours, and subsequently once daily for 14 days. Body weight, mortality, and clinical signs-including behavior (salivation, coat condition, eyes, lethargy, and sleep), changes in appearance, trauma, pain, and other pathological signs-were monitored once daily throughout the observation period. At the end of the 14-day period, all surviving animals were sacrificed, and the major organs (liver, kidneys, spleen, heart, and lungs) were excised, weighed, and examined macroscopically for any abnormalities.

Subchronic oral toxicity assessment

The repeated-dose toxicity of S-Men was assessed over 90 days, in accordance with OECD Guideline 408.[7] *Wistar* rats were divided into three groups (ten rats per group):

- Normal control group: Received vehicle (10 mL/kg/day).

- S-Men-treated group 1: Received S-Men at 1096 mg/kg/day (clinical equivalent dose).

- S-Men treated group 2: Received S-Men at 3288 mg/kg/day (three times the clinical dose).

Rats were dosed orally once daily in the morning for 12 weeks.

Evaluation parameters:

- General condition and body weight: Monitored throughout the study.

- Hematological parameters: Assessed red blood cell count (RBC), mean corpuscular volume (MCV), hemoglobin (Hb), hematocrit (Hct), white blood cell count (WBC), differential leukocyte count, and platelet count (PLT).

- Biochemical parameters: Measured serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol (TC), albumin (ALB), total bilirubin (TBIL), and creatinine (CREA) to evaluate liver and kidney function.

- These parameters were evaluated at the following time points: before the study, and after 4 weeks, 8 weeks, and 12 weeks.

- Histopathology: After 12 weeks, all rats were euthanized for gross organ examination. Liver and kidney tissues from three randomly selected rats per group were analyzed microscopically for structural damage and scored according to standardized criteria.

Data analysis

All data were analyzed using Microsoft Excel 2010 and SPSS version 22.0 with appropriate statistical tests. Results are expressed as mean ± SD. Differences were considered statistically significant when $p < 0.05$.

3. Ethical considerations

The study adhered to strict ethical guidelines for animal research. The authors declare that they have no conflict of interest.

III. RESULTS

1. Acute toxicity assessment of S-Men

General condition

Throughout the 14-day observation period, rats in both the control group and the group receiving S-Men at 5000 mg/kg exhibited normal behavior, including agility, bright eyes, glossy fur, good appetite, and normal dry feces. No abnormal clinical sign was observed in any rats during the study. No mortality was recorded in any group, and thus, testing was concluded at the 5000 mg/kg dose, with no need to evaluate lower doses.

Body weight changes

Table 1. Effect of S-Men on rat body weight

Time point	Body weight (gam)	
	Normal control	S-MEN 5000 mg/kg
Before dosing	173.33 ± 15.28	166.67 ± 30.55
After 14 days	200.00 ± 10.00*	190.00 ± 26.46*
p (before vs. after)	< 0.05	< 0.05

** p < 0.05; ** p < 0.01; *** p < 0.001 compared with before dosing (Paired-samples t-test).*

Table 1 shows that body weight increased significantly ($p < 0.05$) in both the control and S-Men 5000 mg/kg groups after 14 days. No significant difference in weight gain was observed between the control and test groups ($p > 0.05$).

Table 2. Effect of S-Men on organ weights

Organ weight (g/100 g b.w.)	Normal control	S-MEN 5000 mg/kg
Liver	3.55 ± 0.38	3.35 ± 0.29
Kidney	0.70 ± 0.21	0.58 ± 0.07
Spleen	0.34 ± 0.07	0.36 ± 0.01

Organ weight (g/100 g b.w.)	Normal control	S-MEN 5000 mg/kg
Heart	0.31 ± 0.02	0.38 ± 0.05
Lung	0.86 ± 0.11	0.80 ± 0.22

 # p < 0.05 compared with the normal control (Student's t-test).

Table 2 indicates no significant difference in organ weights (liver, kidney, spleen, heart, lung) between the S-Men 5000 mg/kg group and the control group (p > 0.05).

2. Subchronic toxicity assessment of S-Men

General condition and body weight changes

Table 3. Effect of S-Men on rat body weight over 12 weeks

Group	n	Body weight (g)			
		Before dosing	After 4 weeks	After 8 weeks	After 12 weeks
Normal control	10	206.00 ± 27.57	238.00 ± 23.00***	267.00 ± 28.69**	280.80 ± 35.59***
Group 1 (S-Men 1096 mg/kg/day)	10	200.00 ± 22.11	234.00 ± 28.75***	251.00 ± 36.95***	274.00 ± 35.34***
Group 2 (S-Men 3288 mg/kg/day)	10	206.00 ± 15.06	250.00 ± 33.67***	275.00 ± 34.72***	295.00 ± 35.36***

 # p < 0.05 compared with the normal control (Student's t-test).

* p < 0.05; ** p < 0.01; *** p < 0.001 compared with before dosing (paired-samples t-test).

Table 3 shows significant body weight increases (p < 0.05) in all groups (Normal control, Group 1, and Group 2) over 12 weeks. No significant difference in body weight were observed between the test groups and the control group at any time point (p > 0.05).

Hematological parameters

Table 4. Effect of S-Men on red blood cell parameters

Parameter	Time point	Normal control	Group 1 (S-Men 1096 mg/kg/day)	Group 2 (S-Men 3288 mg/kg/day)
RBC (T/L)	T0	8.95 ± 1.47	8.52 ± 1.40	9.19 ± 1.43
	T4	8.55 ±0.94	8.61 ± 1.04	8.88 ± 0.87
	T8	8.40 ± 1.01	7.57 ± 1.10	8.34 ± 0.78
	T12	9.46 ± 1.61	8.65 ± 1.92	9.02 ± 1.16

Parameter	Time point	Normal control	Group 1 (S-Men 1096 mg/kg/day)	Group 2 (S-Men 3288 mg/kg/day)
Hemoglobin (g/L)	T0	12.40 ± 1.67	11.18 ± 1.97	11.97 ± 1.81
	T4	11.03 ± 1.40	11.29 ± 1.36	11.59 ± 0.97
	T8	11.23 ± 1.06	10.59 ± 1.67	10.51 ± 1.48
	T12	11.98 ± 1.49	11.36 ± 1.32	11.39 ± 1.62
Hematocrit (L/L)	T0	45.83 ± 7.95	43.92 ± 7.15	44.89 ± 3.27
	T4	43.69 ± 3.53	43.69 ± 5.28	44.60 ± 3.44
	T8	42.91 ± 4.56	41.11 ± 4.79	42.15 ± 4.16
	T12	44.35 ± 6.51	44.32 ± 5.14	43.15 ± 6.40

Data presented as mean ± SD, . T0: before dosing; T4: 4 weeks; T8: 8 weeks; T12: 12 weeks.

# $p < 0.05$ compared with the normal control (Student's t-test).

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ compared with before dosing (paired-samples t-test).

Table 4 demonstrates that red blood cell count, hemoglobin, and hematocrit in the S-Men groups showed no significant difference compared to the control group at any time point ($p > 0.05$).

Table 5. Effect of S-Men on white blood cell and platelet parameters

Parameter	Time point	Normal control	Group 1 (S-Men 1096 mg/kg/day)	Group 2 (S-Men 3288 mg/kg/day)
WBC (G/L)	T0	9.84 ± 2.23	9.83 ± 1.64	10.43 ± 1.94
	T4	8.97 ± 1.38	9.24 ± 1.85	9.37 ± 1.52
	T8	9.64 ± 1.48	10.56 ± 1.30	10.96 ± 2.21
	T12	10.52 ± 2.39	10.42 ± 1.86	10.73 ± 1.98
Neutrophils (%)	T0	13.45 ± 4.30	13.26 ± 3.15	13.64 ± 3.25
	T4	14.10 ± 3.60	15.12 ± 4.30	15.22 ± 4.15
	T8	14.94 ± 4.20	14.70 ± 4.06	14.84 ± 4.06
	T12	14.15 ± 4.30	14.30 ± 4.30	13.40 ± 3.30
Lymphocytes (%)	T0	72.69 ± 4.62	72.90 ± 3.23	72.78 ± 3.14
	T4	71.35 ± 3.75	70.38 ± 5.34	69.63 ± 4.97
	T8	70.14 ± 6.69	71.67 ± 4.51	69.16 ± 4.90
	T12	71.14 ± 5.70	73.05 ± 7.14	71.14 ± 5.70

Parameter	Time point	Normal control	Group 1 (S-Men 1096 mg/kg/day)	Group 2 (S-Men 3288 mg/kg/day)
Platelets (G/L)	T0	557.40 ± 97.23	500.40 ± 108.69	542.00 ± 89.48
	T4	516.10 ± 91.29	535.00 ± 104.19	485.60 ± 71.56
	T8	557.10 ± 78.62	565.40 ± 125.86	527.00 ± 96.84
	T12	602.20 ± 100.74	525.90 ± 93.34	539.40 ± 96.82

Data presented as mean ± SD, . T0: before dosing; T4: 4 weeks; T8: 8 weeks; T12: 12 weeks.

[#] $p < 0.05$ compared with the normal control (Student's t-test).

** $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ compared with before dosing (paired-samples t-test).*

Table 5 indicates no significant difference in white blood cell count, neutrophil percentage, lymphocyte percentage, or platelet count between the S-Men groups and the control group at any time point ($p > 0.05$).

Biochemical parameters

Table 6. Effect of S-Men on liver and kidney biochemical markers

Parameter	Time point	Normal control	Group 1 (S-Men 1096 mg/kg/day)	Group 2 (S-Men 3288 mg/kg/day)
AST (U/L)	T0	69.70 ± 13.46	62.30 ± 11.57	67.20 ± 11.24
	T4	71.00 ± 14.34	63.20 ± 17.57	69.20 ± 10.41
	T8	60.10 ± 15.32	52.70 ± 11.43	57.30 ± 10.57
	T12	57.70 ± 12.84	60.10 ± 15.50	59.30 ± 11.05
ALT (U/L)	T0	41.30 ± 8.29	41.80 ± 7.45	42.80 ± 8.00
	T4	42.40 ± 10.28	42.80 ± 9.38	46.40 ± 8.75
	T8	36.30 ± 10.46	36.90 ± 7.46	36.90 ± 6.90
	T12	40.70 ± 8.06	37.60 ± 7.01	37.60 ± 7.38
Total Bilirubin (mmol/L)	T0	6.92 ± 0.54	7.03 ± 0.62	6.87 ± 0.78
	T4	7.23 ± 1.21	7.15 ± 0.71	6.93 ± 0.78
	T8	7.00 ± 0.72	7.11 ± 0.75	7.39 ± 0.85
	T12	7.20 ± 1.08	7.19 ± 1.00	7.06 ± 0.86
Albumin (g/dl)	T0	2.46 ± 0.22	2.40 ± 0.16	2.48 ± 0.16
	T4	2.26 ± 0.13	2.23 ± 0.19	2.34 ± 0.22
	T8	2.60 ± 0.09	2.54 ± 0.16	2.58 ± 0.11
	T12	2.58 ± 0.24	2.47 ± 0.16	2.47 ± 0.28

Parameter	Time point	Normal control	Group 1 (S-Men 1096 mg/kg/day)	Group 2 (S-Men 3288 mg/kg/day)
Total Cholesterol (mg/dl)	T0	45.41 ± 9.75	42.75 ± 3.88	46.67 ± 10.27
	T4	46.07 ± 3.91	41.59 ± 6.07	45.24 ± 10.07
	T8	45.26 ± 5.36	42.16 ± 8.06	45.00 ± 7.51
	T12	44.07 ± 5.82	41.09 ± 3.58	42.67 ± 6.20
Creatinin (mmol/L)	T0	66.00 ± 5.25	62.00 ± 4.85	62.80 ± 6.61
	T4	68.00 ± 7.97	67.40 ± 11.80	66.30 ± 5.83
	T8	67.80 ± 8.16	67.70 ± 12.10	67.20 ± 5.92
	T12	70.30 ± 6.75	65.00 ± 7.38	66.50 ± 4.14

Data presented as mean ± SD, . T0: before dosing; T4: 4 weeks; T8: 8 weeks; T12: 12 weeks).

# $p < 0.05$ compared with the normal control (Student's t-test).

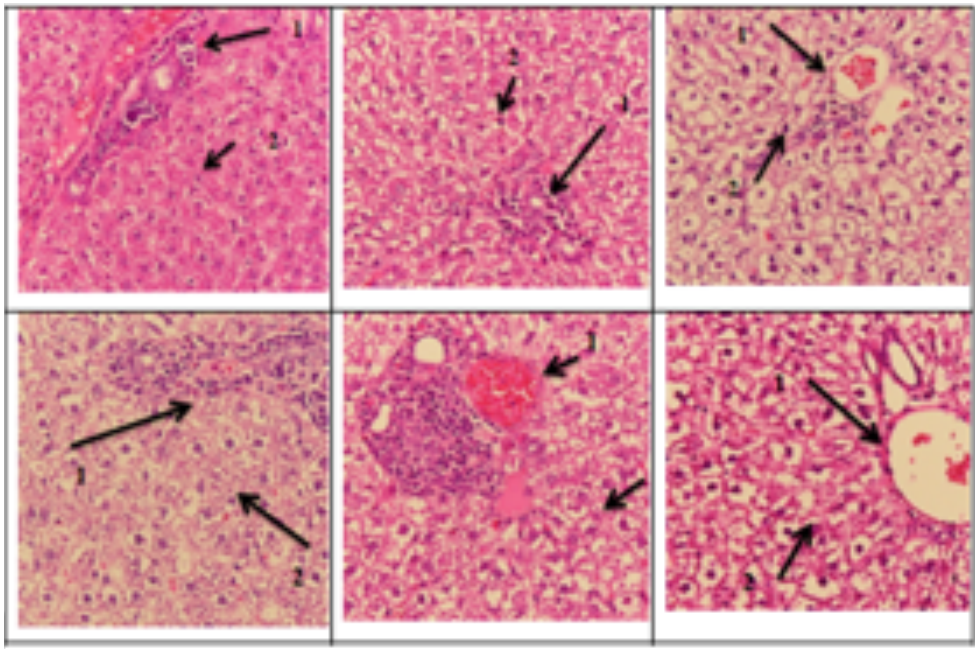
** $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ compared with before dosing (paired-samples t-test).*

Table 6 shows that AST, ALT, total bilirubin, albumin, total cholesterol, and creatinine levels in the S-Men groups were not significantly different from the control group at any time point ($p > 0.05$).

Gross and histopathological observations

Gross Morphology: No pathological change was observed in the heart, lungs, liver, spleen, pancreas, kidneys, or digestive system in any group (Normal control, Group 1, or Group 2) after 12 weeks.

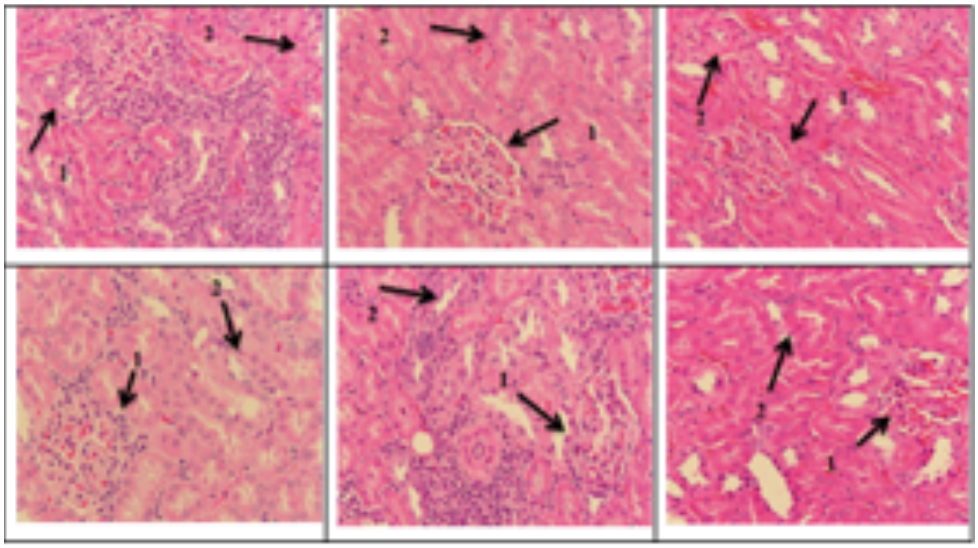
Histopathology of Liver and Kidney: Microscopic examination of liver and kidney tissues (HE, 400x magnification) revealed no difference in structural damage between the control and test groups. Liver images showed normal central veins and hepatocytes, and kidney images showed intact Bowman's capsules and renal tubules across all groups.



Normal control | Group 1 (S-Men 1096 mg/kg/day) | Group 2 (S-Men 32882 mg/kg/day)

Figure 1. Effect of S-Men on liver histopathology

1. Central vein, 2. Hepatocytes



Normal control | Group 1 (S-Men 1096 mg/kg/day) | Group 2 (S-Men 3288 mg/kg/day)

Figure 2. Effect of S-Men on kidney histopathology

1. Bowman's capsule, 2. Renal tubules

IV. DISCUSSION

The evaluation of acute and subchronic toxicity is critical for determining the safety profile of functional products, particularly those intended for reproductive health support. The OECD 423 and OECD 408 guidelines provide robust frameworks for assessing acute and 90-day repeated-dose oral toxicity, offering essential evidence on tolerable doses, potential cellular or organ damage, and impacts on physiological and metabolic functions in experimental animals.[6,7]

The acute toxicity study of S-Men, conducted using the OECD 423 method, demonstrated that a single oral dose of up to 5000 mg/kg did not result in mortality or clinical signs of toxicity. Body weight increased slightly over 14 days, and no gross abnormality was observed in vital organs such as the liver, kidneys, heart, lungs, or spleen. These findings indicate that the LD_{50} of S-Men exceeds 5000 mg/kg, classifying it as having a wide safety margin for acute exposure.

The 12-week subchronic toxicity study, following OECD 408, evaluated S-Men at doses of 1096 mg/kg/day (clinical equivalent) and 3288 mg/kg/day (three times the clinical dose). Comprehensive clinical and laboratory assessments revealed no adverse effect. Rats in all groups displayed normal behavior, including movement, feeding, and appearance of skin, fur, eyes, and feces, with body weight increasing over time but showing no significant difference between the S-Men-treated and control groups ($p > 0.05$).

Hematological parameters are sensitive indicators of toxicity, as the hematopoietic system is vital yet susceptible to toxic substances.[8,9] In this study, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, white blood cell count, differential leukocyte counts (neutrophils and lymphocytes), and platelet counts showed no significant difference between the S-Men and control groups across the 4-, 8-, and 12-week time points ($p > 0.05$). These results suggest that S-Men does not impair hematopoiesis, cause anemia, or disrupt primary immune functions.

Liver and kidney function assessments are central to subchronic toxicity studies, as these organs are primary sites for drug metabolism and excretion.[8–10] Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are key markers of liver damage, with elevated levels indicating hepatocellular injury.[10] Similarly, total bilirubin, albumin, and cholesterol reflect liver metabolic and synthetic functions, while creatinine is a reliable indicator of kidney filtration capacity.[11] After 12 weeks, no significant difference in ALT, AST, total bilirubin, albumin, cholesterol, or creatinine were observed between the S-Men-treated groups and the control group ($p > 0.05$), indicating no adverse effect on liver or kidney function. Histopathological analysis further confirmed the absence of structural damage in liver and kidney tissues, reinforcing the safety of S-Men.

Previous studies on the individual components of S-Men support these findings. Myo-inositol, a key ingredient, was evaluated by Smith et al. at 5000 mg/kg/day for 14 days in *Wistar* rats, showing no mortality, clinical abnormality, or change in hematological, biochemical, or histopathological parameters.[12] L-carnitine, studied by Greff et al. (2023) in clinical trials, was well-tolerated with no significant liver or kidney toxicity at typical doses.[12] A long-term study by Silva et al. (2019) on L-carnitine at 50 mg/kg/day for 7 months in *Wistar* rats reported increased tissue carnitine levels, reduced oxidative stress, and no abnormal histopathological or

biochemical change in liver, kidney, stomach, or testes.[13] Similarly, Tizhe et al. (2013) found that zinc supplementation for 90 days in *Wistar* rats caused no significant hematological, biochemical, or histopathological change at moderate doses.[14] Daragó et al. (2020) demonstrated that combined zinc and selenium supplementation for 90 days in male rats had no notable liver or kidney toxicity, further supporting the safety of these components.[15]

Collectively, these data indicate that S-Men is highly safe, showing no acute toxicity at doses up to 5000 mg/kg and no subchronic toxicity at doses up to 3288 mg/kg/day over 12 weeks. Hematological, biochemical, and histopathological parameters remained within normal limits. Supported by existing literature, S-Men appears safe for male reproductive support. Future clinical studies should explore longer-term effects and additional endpoints, such as endocrine function, reproductive outcomes, and oxidative stress markers, to further validate its safety profile.

V. CONCLUSION

S-Men, administered orally to *Wistar* rats at 5000 mg/kg, showed no acute toxicity, with an LD_{50} exceeding 5000 mg/kg, classifying it as non-toxic according to OECD 423 [6]. In a 12-week subchronic study at 1096 and 3288 mg/kg/day, S-Men caused no adverse effect on body weight, hematological or biochemical parameters, or liver/kidney histopathology. S-Men exhibits a high safety profile in both acute and subchronic oral toxicity studies in *Wistar* rats, providing critical preclinical data to guide dosing and support further clinical investigations for its use in male reproductive health.

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