© 2024 Journal of Pharmacy & Pharmacognosy Research, 12 (2), 363-370, 2024
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres23.1852_12.2.363

*Original Article*

# Toxicity of sibutramine hydrochloride-adulterated weight loss supplements in rats based on biochemical and organ weight parameters

[Toxicidad de los suplementos de pérdida de peso adulterados con clorhidrato de sibutramina en ratas según parámetros bioquímicos y de peso de órganos]

**Suparmi Suparmi[1*], Suryani Yuliyanti[2], Hesti W. Karyadini[3], Andi M.R. Syamsudin[4], Edil Kurniawan Gau[4]**

[1]Department of Biology, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, 50112, Indonesia.
[2]Department of Public Health, Faculty of Medicine, Universitas Islam Sultan Agung Semarang, 50112, Indonesia.
[3]Department of Dermatology and Venereology Faculty of Medicine, Universitas Islam Sultan Agung Semarang, 50112, Indonesia.
[4]Study Program of Medical Education, Faculty of Medicine, Universitas Islam Sultan Agung Semarang, 50112, Indonesia.
*E-mail: suparmi@unissula.ac.id

## Abstract

*Context*: Weight-loss supplements are typically natural or herbal supplements that promote weight loss and enhance health. However, the increase in consumption results in the fraudulent adulteration of conventional pharmaceutical drugs, such as sibutramine hydrochloride (SHCl).

*Aims*: To determine the toxicity of weight loss supplements adulterated with SHCl in rats.

*Methods*: Five samples (J1–J5) of weight loss supplements adulterated with SHCl were collected from an online market. The toxicity of the samples was evaluated using 42 male Wistar rats for 35 days. The rats were divided into seven groups: control, J1, J2, J3, J4, J5, and SHCl.

*Results*: The J1 supplement resulted in the most rapid weight loss in rats compared to the other supplements tested. The kidney and liver weights of rats administered weight loss supplements adulterated with SHCl were greater than those of control rats. J1 indicated the supplement with the highest level of toxicity. The group administered J1 exhibited the highest levels of toxicity across all evaluated parameters.

*Conclusions*: This study confirmed the toxicity of weight loss supplements adulterated with SHCl in rats, contributing to the understanding and treatment of adulterated weight loss supplements. Dietary supplements for weight loss should be thoroughly screened for undeclared sibutramine hydrochloride adulteration to protect public health and strengthen legal provisions.

*Keywords*: adulteration; hepatotoxicity; kidney toxicity; sibutramine hydrochloride; weight loss supplements.

## Resumen

*Contexto*: Los suplementos para adelgazar suelen ser complementos naturales o a base de hierbas que favorecen la pérdida de peso y mejoran la salud. Sin embargo, el aumento de su consumo provoca la adulteración fraudulenta de fármacos convencionales, como el clorhidrato de sibutramina (SHCl).

*Objetivos*: Determinar la toxicidad de los suplementos para adelgazar adulterados con SHCl en ratas.

*Métodos:* Se recogieron cinco muestras (J1-J5) de suplementos para adelgazar adulterados con SHCl en un mercado online. La toxicidad de las muestras se evaluó con 42 ratas Wistar macho durante 35 días. Las ratas se dividieron en siete grupos: control, J1, J2, J3, J4, J5 y SHCl.

*Resultados*: El suplemento J1 provocó la pérdida de peso más rápida en las ratas en comparación con los demás suplementos probados. Los pesos del riñón y el hígado de las ratas a las que se administraron suplementos adelgazantes adulterados con SHCl fueron superiores a los de las ratas de control. J1 indicó el suplemento con el mayor nivel de toxicidad. El grupo al que se administró J1 mostró los niveles más altos de toxicidad en todos los parámetros evaluados.

*Conclusiones*: Este estudio confirmó la toxicidad de los suplementos para adelgazar adulterados con SHCl en ratas, contribuyendo a la comprensión y tratamiento de los suplementos para adelgazar adulterados. Los suplementos dietéticos para la pérdida de peso deben ser examinados minuciosamente para detectar adulteraciones no declaradas con clorhidrato de sibutramina, con el fin de proteger la salud pública y reforzar las disposiciones legales.

*Palabras Clave*: adulteración; hepatotoxicidad; sibutramina clorhidrato; suplementos para adelgazar; toxicidad renal.

ARTICLE INFO
Received: October 17, 2023.
Accepted: December 24, 2023.
Available Online: December 30, 2023.

AUTHOR INFO
ORCID: 0000-0001-7914-870X (SS)
0000-0002-4750-6231 (SY)

## INTRODUCTION

Weight loss supplements and proprietary slimming products are frequently plant food supplements (PFS) intended to promote weight loss and health improvement. The public's reliance on "quick-fix" slimming agents is rising as it seeks more straightforward weight control methods. Consequently, various proprietary products with a purported weight-loss effect are now on the market. However, to create instant pharmacological reactions or enhance the supplement's biological action, some products are made with the deliberate addition of pharmaceuticals, which is called economically motivated adulteration (EMA) (Aghahowa et al., 2021; Calahan et al., 2016; Momtaz et al., 2023; Nasution and Suyanto, 2022). In pharmaceutical adulteration, an active drug, such as sibutramine, is added to a purportedly botanical supplement (Firozian et al., 2021; Jairoun et al., 2021). These items are frequently advertised as containing only natural ingredients, so they are considered safe. In addition, they are widely available without prescription and are often inexpensive.

Sibutramine hydrochloride (SHCl) is added to weight-loss dietary supplements because it utilizes noradrenaline and serotonin reuptake inhibitors, causing increases in the synaptic concentration of these neurotransmitters and activating adrenoceptors, adrenoceptors, and serotonin receptors. These chemical effects cause individuals to feel fuller and expend more energy, resulting in weight loss (Hayun et al., 2016; Kaya et al., 2004; Tang et al., 2011). Consuming illegal SHCl additives in excessive amounts poses additional health risks, and consumers may be unaware of what they are taking (Jordan et al., 2010; Kozhuharov et al., 2022).

Depending on the dosage, the harmful side effects of SHCl include dry mouth, headaches, insomnia, constipation, hepatitis, psychosis, arrhythmia, and severe cardiovascular disturbances (Anyanwu et al., 2020; Chen et al., 2010; Jung et al., 2006). The most significant risk associated with sibutramine is its ability to increase blood pressure and heart rate; consequently, a large proportion of obese patients also have cardiovascular morbidity. These cautions prohibit the use of SHCl in obese individuals (Furman, 2007; Nelson and Gehlert, 2007; Willson, 2019; Wooltorton, 2002). All 12 patients developed acute liver injury characterized by a significant increase in serum liver chemistry values (mean alanine aminotransferase level, 1978 U/L [range, 283 to 4074 U/L]) after ingesting the Japanese-marketed Chinese herbal weight loss supplements Chaso and Onshido. Two patients developed fulminant hepatic failure, one of whom required a liver transplant and the other of whom passed away (Adachi et al., 2003).

The worldwide license permits SHCL use at a dosage of 10 to 15 mg per day. However, its commercial reach has been restricted due to concerns over cardiovascular side effects (Arterburn et al., 2004; Kim et al., 2016). In March 2002, the Italian regulatory authority temporarily halted the market authorization of sibutramine due to 50 adverse reactions, including two deaths connected to cardiovascular issues. The European Committee for Proprietary Medicinal Products and the Health Sciences Authority (HSA) reported that the risk for an adverse cardiovascular outweighed any benefit from the weight loss observed with the SHCL (HSA, 2023). Due to several safety concerns, a consumer group has submitted a petition to the Food and Drug Administration (FDA), urging them to prohibit the sale of sibutramine in the United States. The FDA's Sibutramine Cardiovascular Outcomes (SCOUT) trial reported that patients treated with Meridia (sibutramine) had a 16% higher risk of experiencing major adverse cardiovascular events, such as non-fatal heart attack, non-fatal stroke, resuscitation after cardiac arrest, and cardiovascular death, compared to patients who were given a placebo (FDA, 2018). According to Regulation of BPOM RI (*Badan Pengawas Obat dan Makanan Republik Indonesia*/National Agency for Drug and Food Control Republic of Indonesia, NADFC RI) No. 19/2021 on the Monitoring of Harmful Effects of Traditional Medicines, Curative Drugs, Health Supplements and Cosmetics, the use of sibutamine is prohibited in Indonesia because it causes side effects such as increased blood pressure and heart rate and difficulty sleeping (BPOM-RI, 2006).

In light of these facts and the lack of scientific research in this field in Indonesia, this study hypothesized that SHCl-adulterated herbal weight loss supplements sold in Indonesia cause liver and kidney toxicity. This study aimed to assess the subacute toxicity of the weight loss supplement containing SHCl. The findings will aid in establishing the need for regulatory bodies to develop a risk assessment module for the safety of weight loss supplements.

## MATERIAL AND METHODS

### Collection and preparation of samples

Five samples (J1-J5) of weight loss supplements adulterated with sibutramine hydrochloride (SHCl) were collected from an online retailer (Table 1). Targeted sampling was conducted based on a report from the Republic of Indonesia's National Agency for

**Table 1.** Listing of treated SHCL-adulterated weight loss supplements according to sample characteristics and prescription label.

| Sample code | Ingredients | Recommended daily consumption | Daily dose for woman (mg/kg/BW) | Converted dose from human to rats (mg/kg/BW)* |
|---|---|---|---|---|
| J1 | *Glycyrrhizae radix* 150 mg, *Guazuma folium* 150 mg, *Parameria barbta* 50 mg, *Grategi fructus* 100 mg, *Punica granatum* 50 mg | 3x1 a day | 120 | 2.16 |
| J2 | White kidney bean extract, *Garcinia cambogia* and L-carnitine. | 1-2 capsules a day after lunch/dinner | 80 | 1.44 |
| J4 | Green coffee extract, chlorogenic acid, caffeine, polyphenol, quinic acid, cellulose, Etc. | 2x1 capsules before lunch and dinner | 38 | 0.68 |
| J5 | Shell and crab shell extract: chitin. | 2x1 a day | 80 | 1.44 |
| J6 | Undeclared | 1-2 capsules a day after lunch/dinner | 80 | 1.44 |
| SHCl | Sibutramine HCl 15 mg | 2x1 a day | 80 | 1.44 |

*The conversion factor from humans to rats was 0.018.

Drug and Food Control (BPOM-RI)(BPOM-RI, 2018) regarding adulteration in traditional medicine sold in Indonesia.

The capsules were homogenized using a mortar, pestle, and grinder to create fine powders. The homogenized substance was then used to prepare samples. The powders were homogenized and then incorporated into the treated weight loss supplement by stirring with a homogenizer.

## Experimental animals

Male Wistar rats with a body weight range of 179 ± 4 g were used in this study. Each rat was acclimated for one week in an environmentally controlled room at an ambient temperature of 25°C, 50 ± 10% humidity, air ventilation of 10~15 times/h, and a light/dark cycle of 12 h in cages. Throughout the experiment, they had unrestricted access to regular food and water. The animal study protocol was approved by the Institutional Review Board (or Ethics Committee) of the Faculty of Medicine, Universitas Islam Sultan Agung (Ethical Clearance No. 282/VIII/2021/Komisi Bioetik and date of approval on 30 August 2021).

The 42 male rats were randomly divided into seven groups of six. The control group was administered aquadest as the treatment solvent, which was considered a negative control. Five weight loss supplements adulterated with sibutramine samples were administered to groups J1 through J5; the SHCl group served as a positive control. The dose of each supplement listed in Table 1 was administered orally once daily for 35 consecutive days. Throughout the study period, weekly body weight measurements were taken. Body weight change was calculated from the differences between the initial treatment (day 1) and final treatment (day 36).

## Determination of biochemical and organ weight parameters

After the experiment, the rats were transferred to individual metabolic cages, urine was collected on ice in 50 mL polypropylene tubes containing 1 mL of 1% sodium azide, and the urine pH was measured. Blood samples were drawn from the orbital sinus using heparinized tubes for hematological analyses and non-heparinized tubes for serum separation via centrifugation at 3000 rpm for 10 minutes and then used for biochemical analyses.

We used a clinical chemistry analyzer (HITACHI 7020) and an assay kit for each enzyme to measure the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid, albumin, bilirubin, creatinine, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) in the blood.

Animals were sacrificed under light anesthesia of ether. The weights of the organs (liver and kidneys) were recorded following the sacrifice.

## Statistical analysis

Data were expressed as means ± SD. Statistical analyses and the comparison of means were evaluated using ANOVA (Tukey's test). The differences were considered statistically significant at $p<0.05$. Analyses were performed with GraphPad Prism version 8.3.1 (332) (San Diego, CA, USA).

**Table 2.** Body weight changes, kidneys, and liver weight of control and treatment groups after five weeks of sibutramine-adulterated weight loss supplements.

| Group | Body weight changes (g) | Liver (g) | Right kidney (g) | Left kidney (g) |
|---|---|---|---|---|
| Control | 34.50 ± 1.05 | 6.20 ± 0.48 | 0.68 ± 0.05 | 0.68 ± 0.05 |
| J1 | 22.83 ± 1.47 | 7.80 ± 0.56 | 0.75 ± 0.03 | 0.75 ± 0.03 |
| J2 | 22.50 ± 1.05 | 7.50 ± 0.87 | 0.82 ± 0.05 | 0.82 ± 0.05 |
| J3 | 22.67 ± 1.03 | 7.67 ± 0.44 | 0.85 ± 0.03 | 0.86 ± 0.03 |
| J4 | 23.17 ± 0.75 | 7.02 ± 0.08 | 0.83 ± 0.03 | 0.83 ± 0.04 |
| J5 | 22.17 ± 1.33 | 7.06 ± 0.11 | 0.78 ± 0.07 | 0.82 ± 0.05 |
| SHCL | 22.83 ± 1.47 | 7.98 ± 0.52 | 0.79 ± 0.04 | 0.79 ± 0.04 |

## RESULTS

### Body weight changes and organ weight

The body weight change of rats treated with the five samples (J1-J5) of weight loss supplements adulterated with sibutramine was significantly different ($p<0.05$) from the control group but not significantly different ($p>0.05$) to the SHCL group as the positive control (Table 2). The administration of sibutramine-adulterated weight loss supplements for 35 days led to a significant increase in kidney and liver weight compared to the control group. However, kidney and liver weight did not significantly differ ($p>0.05$) between the treated sibutramine-adulterated supplement (J1-J5) and sibutramine hydrochloride (SHCl) groups.

### Biochemical parameters for liver toxicity

Compared to the control group, rats treated with sibutramine-adulterated weight loss had significantly elevated levels of all biomarkers of liver toxicity tested. The levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) were significantly increased by J1 and J2 (Fig. 1).

### Biochemical parameters for kidney toxicity

Concerning uric acid levels, the rats treated with sibutramine HCl-adulterated weight loss supplements showed a significant increase compared to the control group, while the urine pH decreased. Similarly, administration of sibutramine at a dose of 1.44 mg/kg BW/day did not result in a statistically significant difference ($p>0.05$) in urine pH values (Fig. 2).

In rats treated with sibutramine HCl-adulterated weight loss supplements, the levels of creatinine and urea increased (Fig. 3a-b). Concerning albumin levels, all groups of rats treated with the five samples of sibutramine HCl-adulterated weight loss supplement showed a significant decrease compared to the control rats (Fig. 3c). J1 and J2 significantly increased T-bilirubin levels compared to the sibutramine HCl drug (Fig. 3d).

## DISCUSSION

Sibutramine hydrochloride (SHCl), N-{1-[1-(4-chlorophenyl)cyclobut-yl]-3-methylbutyl}-N,N-dimethylamine hydrochloride monohydrate ($C_{17}H_{26}ClN \cdot HCl \cdot H_2O$) that decreases appetite and increases metabolism, represent significant advances in the pharmacological treatment of obesity. SHCl, on the other hand, inhibits the neuronal uptake of serotonin and norepinephrine and acts centrally to control appetite (Nisoli and Carruba, 2000). The Republic of Indonesia's National Agency for Drug and Food Control (BPOM-RI) reported that SHCl has been illegally adulterated with natural herbal medicines and dietary supplements for weight loss. Although products that contain sibutramine have been banned, they can be easily purchased online. This study examined the hepatotoxicity and liver toxicity effect of sibutramine HCl in rats treated with adulterated products.

Hepatotoxicity is one of the most frequent treatment-related changes in experimental animals because the liver is the major organ involved in the metabolism of xenobiotics. In addition, the induction of liver drug-metabolizing enzymes results in liver hypertrophy to increase metabolic capacity. Based on the findings in the body weight changes and the significant increase in the organ weights (Table 1). The rise in liver and kidney weight is due to the increase in the average size of the hepatocytes (hepatocellular hypertrophy) and even hepatic enzyme induction (Ennulat et al., 2010; Hall et al., 2012) caused by consumption of the products.

The biochemistry of liver parameters was measured to determine whether increases in hepatic-derived enzymes accompany hypertrophy. It is well known that serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma-glutamyl transferase (γ-GT) are well-established biochemical markers used for clinical

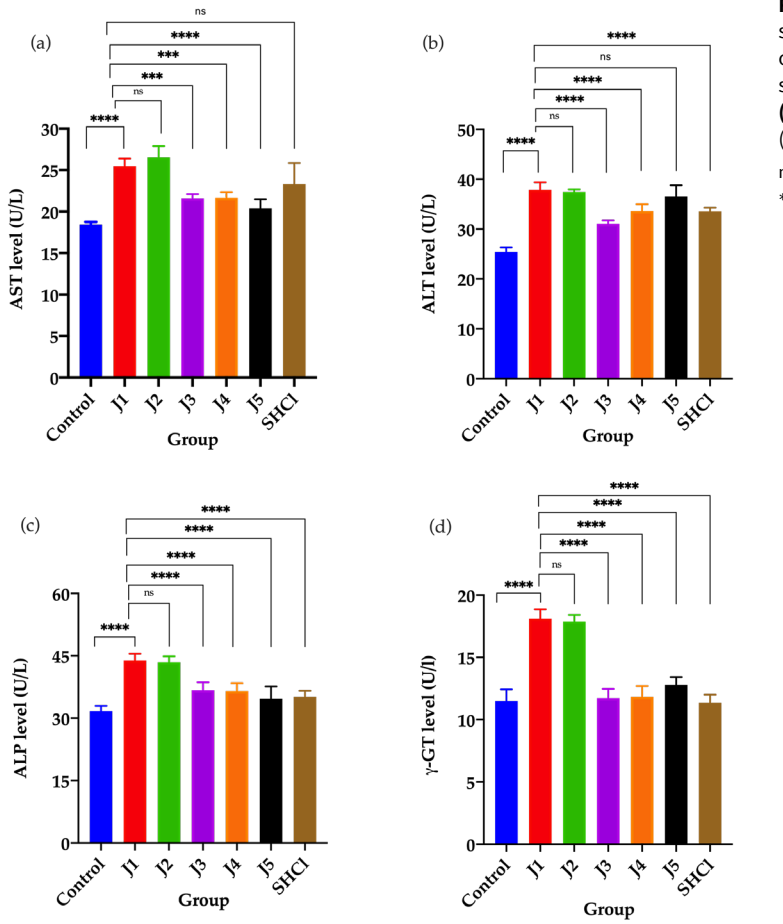


**Figure 1**. Effects of subacute oral administration of sibutramine-adulterated weight loss supplements on the liver toxicity biochemistry parameters in rat serum, including **(a)** AST levels, **(b)** ALT levels, **(c)** ALP levels, and **(d)** gamma-glutamyl transferase (γ-GT).

ns: nonsignificant; ∗p< 0.05; ∗∗p<0.01; ∗∗∗p< 0.001; and ∗∗∗∗p<0.0001 among the compared groups.

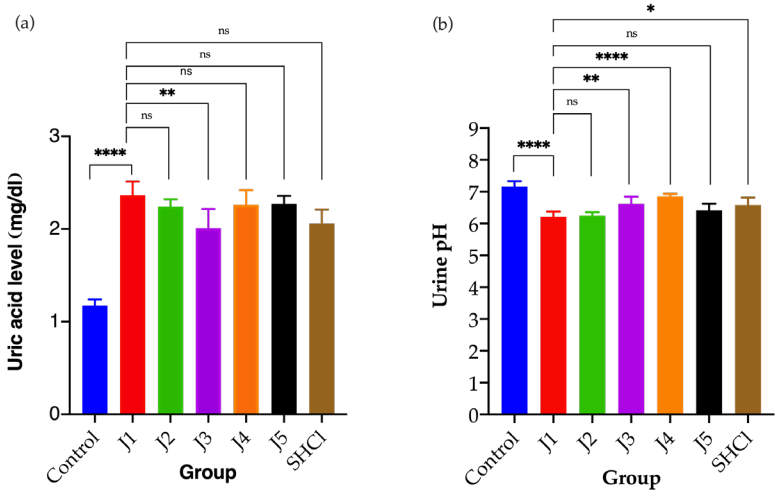


**Figure 2.** Effects of subacute oral administration of sibutramine-adulterated weight loss supplements on kidney toxicity biochemistry parameters in rats, including **(a)** uric acid levels in blood serum and **(b)** urine pH.

ns: nonsignificant; ∗p<0.05; ∗∗p<0.01; ∗∗∗p<0.001; and ∗∗∗∗p< 0.0001 among the compared groups.

diagnosis of liver damage, particularly hepatobiliary damage, in humans and animals of liver diseases (Arneson and Brickell, 2007; Guyton and Hall, 2011; Yokoyama et al., 2019; Zou et al., 2020). This study found deleterious changes in the AST, ALT, ALP, and γ-GT of treated rats (Fig. 1), indicating a hepatotoxicity effect due to the SHCl-adulterated weight loss supplement consumption. Chounta et al. (2005) reported a case of sibutramine-induced liver injury in a 47-year-old woman who presented with a 1-month history of pruritus, fatigue, weakness, and dark urine, beginning two weeks after initiating sibutramine. Nevertheless, no underlying mechanism was proposed.

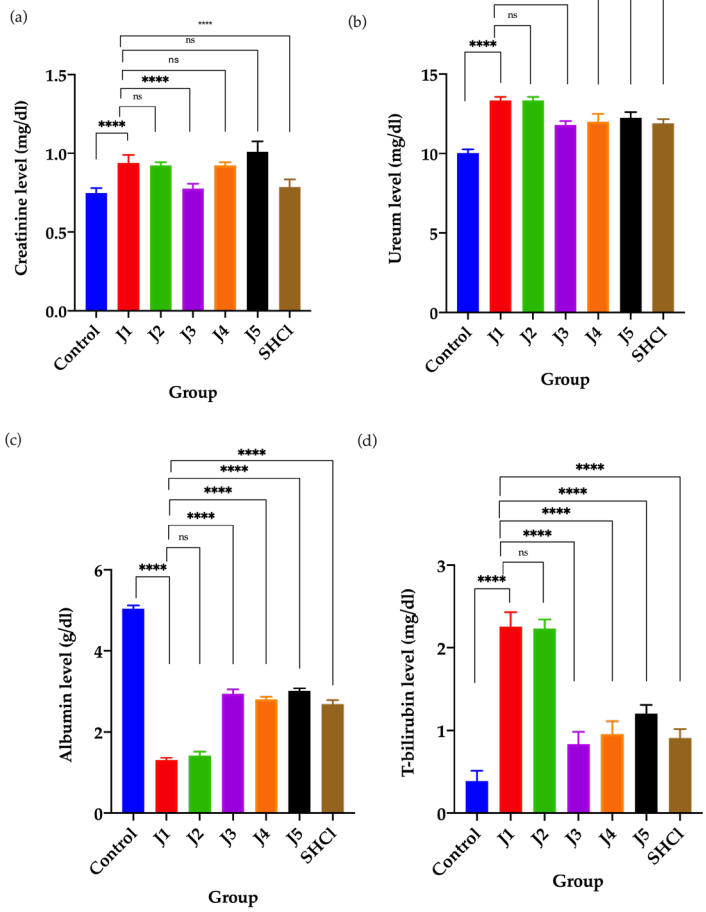


**Figure 3.** Effects of oral administration of sibutramine-adulterated weight loss supplements on kidney toxicity biochemistry parameters in rat serum, including **(a)** creatinine, **(b)** urea, **(c)** albumin, and **(d)** T-bilirubin.

ns: nonsignificant; ∗p< 0.05; ∗∗p< 0.01; ∗∗∗p< 0.001; and ∗∗∗∗p< 0.0001 among the compared groups.

In addition, this study demonstrates the kidney toxicity caused by 35 days of rat consumption of SHCl-adulterated slimming supplements (J1–J5). In all treatment groups, the pH of the kidney's urine decreased, but this was inversely proportional to uric acid levels. Serum levels of creatinine, urea, and T-bilirubin, which are biomarkers of kidney damage (Gowda et al., 2010; Jonker et al., 2012), were significantly increased by the consumption of sibutramine HCl-adulterated weight loss supplements, whereas albumin levels decreased. Changes in biomarkers of kidney damage were more pronounced in J1 and J2 rats, indicating that they were as toxic as sibutramine hydrochloride. These findings suggest that dietary supplements containing sibutramine HCl may cause renal cell damage and glomerular filtration dysfunction in rats, as indicated by changes in kidney damage biomarkers in the kidney or urine. Uncertainty surrounds the mechanism underlying the nephrotoxicity of PS. Further research on nephropathy with mechanistic and specific kidney toxicity biomarkers may explain.

In contrast to the findings of Schoor (2014), who reported that a 28-day administration of 1.32 mg/kg (low dose) and 13.2 mg/kg (high dose) did not affect the biochemical data of liver and kidney function in rats, this study found a significant effect. Sibutramine was more teratogenic than ephedrine, according to in-ovo teratogenic tests conducted with chick embryos. In addition, sibutramine causes cardiac dystrophy and liver steatosis in embryos, resulting in severe liver and heart damage (van der Schoor, 2014). Understanding the mechanisms underlying the pathogenesis of these findings is a crucial area for future research.

This study demonstrated the toxicity of sibutramine-chloride-adulterated weight loss supplements collected from Indonesian online retailers, which did not correspond to the ingredients listed on their labels in most instances. This result was consistent with those (Fard and Akhgari, 2018), who reported that 23 percent of 80 samples of herbal sexual enhancer drugs contained sildenafil; therefore, regular analysis of herbal purported medicines is necessary for more effective quality control and health

promotion. To protect the consumers, the present study's findings demonstrate the importance of vigilance and the implementation of good manufacturing practices in Indonesian herbal products for weight loss.

## CONCLUSION

Our study reveals that a weight loss supplement containing sibutramine that was administered orally to rats for five weeks caused liver and kidney toxicity. Weight loss supplements should be thoroughly screened for undeclared sibutramine hydrochloride adulteration to protect public health and strengthen legal provisions.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## ACKNOWLEDGMENTS

This research was funded by the Faculty of Medicine, Universitas Islam Sultan Agung (UNISSULA) grant number 11/P-KEL/UPR-FK/III/2021 and the Research and Community Service Board of UNISSULA grant number 246/B.1/SA-LPPM/VII/2021.

## REFERENCES

Adachi M, Saito H, Kobayashi H, Horie Y, Kato S, Yoshioka M, Ishii H (2003) Hepatic injury in 12 patients taking the herbal weight loss AIDS Chaso or Onshido. Ann Intern Med 139(6): 488-492. https://doi.org/10.7326/0003-4819-139-6-200309160-00012

Aghahowa SE, Ozolua RI, Bafor EE, Obarisiagbon P, Isah AO (2021) Toxicological effect of artemisinin-based combination therapies plus paracetamol in malaria patients. Toxicol Rep 8: 1930–1936. https://doi.org/10.1016/j.toxrep.2021.11.007

Anyanwu GO, Kolb AF, Bermano G (2020) Chapter 9 - Antiobesity functional leads and targets for drug development. In: Phytochemicals as Lead Compounds for New Drug Discovery. Egbuna C, Kumar S, Ifemeje JC, Ezzat SM, Kaliyaperumal S (Eds.). Elsevier, pp. 143–160. https://doi.org/10.1016/B978-0-12-817890-4.00009-3

Arneson W, Brickell J (2007) Clinical Chemistry, a Laboratory Perspective. Philadelphia: Davis Company.

Arterburn DE, Crane PK, Veenstra DL (2004) The efficacy and safety of sibutramine for weight loss: A systematic review. Arch Intern Med 164(9): 994–1003. https://doi.org/10.1001/archinte.164.9.994

BPOM-RI (2006) Bahaya Bahan Kimia Obat (BKO) yang Dibubuhkan Kedalam Obat Tradisional (Jamu). https://www.pom.go.id/berita/bahaya-bahan-kimia-obat-(bko)-yang-dibubuhkan-kedalam-obat-tradisional-(jamu). [Accessed 12 June 2023].

BPOM-RI (2018) Temuan Kosmetik Ilegal dan mengandung Bahan Dilarang/Bahan Berbahaya Serta Obat Tradisional Ilegal dan mengandung Bahan Kimia Obat. In Badan Pengawas Obat dan Makanan. https://www.pom.go.id/new/view/more/pers/443/Temuan-Kosmetik-Ilegal-dan-Mengandung-Bahan-Dilarang-Bahan-Berbahaya-serta-Obat-Tradisional-Ilegal-dan-Mengandung-Bahan-Kimia-Obat.html. [Accessed 12 December 2023].

Calahan J, Howard D, Almalki AJ, Gupta MP, Calderón AI (2016) Chemical adulterants in herbal medicinal products: A review. Planta Med 82: 505–515. https://doi.org/10.1055/s-0042-103495

Chen SP, Tang MH, Ng SW, Poon WT, Chan AY, Mak TW (2010) Psychosis associated with usage of herbal slimming products adulterated with sibutramine: A case series. Clin Toxicol (48): 832–838. https://doi.org/10.3109/15563650.2010.517208

Chounta A, Tsiodras S, Zouridakis S, Doumas M, Giamarellou H (2005) Sibutramine use associated with reversible hepatotoxicity. Ann Intern Med 143: 763–764. https://doi.org/10.7326/0003-4819-143-10-200511150-00030

Ennulat D, Walker D, Clemo F, Magid-Slav M, Ledieu D, Graham M, Botts S, Boone L (2010) Effects of hepatic drug-metabolizing enzyme induction on clinical pathology parameters in animals and man. Toxicol Pathol 38: 810–828. https://doi.org/10.1177/0192623310374332

Fard HH, Akhgari M (2018) Analytical perspectives of chemical adulterants in herbal sexual enhancer drugs. J Pharm Pharmacogn Res 6: 45–53.

Firozian F, Nili-Ahmadabadi A, Moradkhani S, Moulaei M, Fasihi Z, Ahmadimoghaddam D (2021) Adulteration of the herbal weight loss products by the illegal addition of synthetic antiobesity medications: A pilot study. J Obes 2021: 9968730. https://doi.org/10.1155/2021/9968730

Furman BL (2007) Antiobesity Agents. In: xPharm: The Comprehensive Pharmacology Reference. Enna SJ, Bylund DB (Eds.). New York: Elsevier, pp. 1–2. https://doi.org/10.1016/B978-008055232-3.61048-7

Gowda S, Desai PB, Kulkarni SS, Hull VV, Math AA, Vernekar SN (2010) Markers of renal function tests. N Am J Med Sci 2(4): 170–173. https://pubmed.ncbi.nlm.nih.gov/22624135/

Guyton, Hall JE (2011) Buku Ajar Fisiologi Kedokteran, 12th ed. Saunders Elsevier, Amerika Serikat.

Hall AP, Elcombe CR, Foster JR, Harada T, Kaufmann W, Knippel A, Küttler K, Malarkey DE, Maronpot RR, Nishikawa A, Nolte T, Schulte A, Strauss V, York MJ (2012) Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes--conclusions from the 3rd International ESTP Expert Workshop. Toxicol Pathol 40(7): 971-994. https://doi.org/10.1177/0192623312448935

Hayun H, Maggadani BP, Amalina NH (2016) Determination of sibutramine adulterated in herbal slimming products using TLC densitometric method. Indones J Pharm 27: 15–21. http://dx.doi.org/10.14499/indonesianjpharm27iss1pp15

HSA (2023) Health Sciences Authority (HSA) HSA updates on products found overseas that contain potent ingredients (September 2023). https://www.hsa.gov.sg/announcements/safety-alert/hsa-updates-on-products-found-overseas-that-contain-potent-ingredients-(September-2023). [Accessed 12 November 2023].

Jairoun AA, Al-Hemyari SS, Shahwan M, Zyoud SH (2021) Adulteration of weight loss supplements by the illegal addition of synthetic pharmaceuticals. Molecules 26(22): 6903. https://doi.org/10.3390/molecules26226903

Jonker JW, Liddle C, Downes M (2012) FXR and PXR: Potential therapeutic targets in cholestasis. J Steroid Biochem Mol Biol 130: 147–158. https://doi.org/10.1016/j.jsbmb.2011.06.012

Jordan SA, Cunningham DG, Marles RJ (2010) Assessment of herbal medicinal products: Challenges, and opportunities to increase the knowledge base for safety assessment. Toxicol Appl Pharmacol 243: 198–216. https://doi.org/10.1016/j.taap.2009.12.005

Jung J, Hermanns-Clausen M, Weinmann W (2006) Anorectic sibutramine detected in a Chinese herbal drug for weight loss.

Forensic Sci Int 161: 221–222. https://doi.org/10.1016/j.forsciint.2006.02.052

Kaya A, Aydin N, Topsever P, Filiz M, Oztürk A, Dağar A, Kilinç E, Ekmekcioglu C (2004) Efficacy of sibutramine, orlistat and combination therapy on short-term weight management in obese patients. Biomed Pharmacother 58: 582–587. https://doi.org/10.1016/j.biopha.2004.09.006

Kim SH, Chun HJ, Choi HS, Kim ES, Keum B, Jeen YT (2016) Current status of intragastric balloon for obesity treatment. World J Gastroenterol 22(24): 5495–5504. https://doi.org/10.3748/wjg.v22.i24.5495

Kozhuharov VR, Ivanov K, Ivanova S (2022) Dietary supplements as source of unintentional doping. Biomed Res Int 2022: 8387271. https://doi.org/10.1155/2022/8387271

Momtaz M, Bubli SY, Khan MS (2023) Mechanisms and health aspects of food adulteration: A comprehensive review. Foods 12(1): 199. https://doi.org/10.3390/foods12010199

Nasution AMT, Suyanto H (2022) Infrared Spectroscopy for Detecting Adulterants in Food and Traditional Indonesian Herbal Medicine. In: Infrared Spectroscopy - Perspectives and Applications. El-Azazy APM, Al-Saad DK, El-Shafie DAS (Eds.). IntechOpen. https://doi.org/10.5772/intechopen.106803

Nelson DL, Gehlert DR (2007) 6.18 - Obesity/Disorders of Energy. In: Comprehensive Medicinal Chemistry II. Taylor JB, Triggle DJ (Eds.). Oxford: Elsevier, pp. 389–416. https://doi.org/10.1016/B0-08-045044-X/00178-4

Nisoli E, Carruba MO (2000) An assessment of the safety and efficacy of sibutramine, an anti-obesity drug with a novel mechanism of action. Obes Rev 1(2): 127–139. https://doi.org/10.1046/j.1467-789x.2000.00020.x

Tang MH, Chen SP, Ng SW, Chan AY, Mak TW (2011) Case series on a diversity of illicit weight-reducing agents: From the well known to the unexpected. Br J Clin Pharmacol 71: 250–253. https://doi.org/10.1111/j.1365-2125.2010.03822.x

van der Schoor C (2014) An *in vivo* and *in ovo* evaluation of the toxicity of sibutramine. Dissertation (MSc). University of Pretoria.

Willson C (2019) Sympathomimetic amine compounds and hepatotoxicity: Not all are alike—Key distinctions noted in a short review. Toxicol Rep 6: 26–33. https://doi.org/10.1016/j.toxrep.2018.11.013

Wooltorton E (2002) Obesity drug sibutramine (Meridia): Hypertension and cardiac arrhythmias. Can Med Assoc J 166: 1307–1308. https://pubmed.ncbi.nlm.nih.gov/12041851/

Yokoyama Y, Ono A, Yoshida M, Matsumoto K, Saito M (2019) Toxicological significance of increased serum alkaline phosphatase activity in dog studies of pesticides: Analysis of toxicological data evaluated in Japan. Regul Toxicol Pharmacol 109: 104482. https://doi.org/10.1016/j.yrtph.2019.104482

Zou Y, Zhong L, Hu C, Sheng G (2020) Association between the alanine aminotransferase/aspartate aminotransferase ratio and new-onset non-alcoholic fatty liver disease in a nonobese Chinese population: A population-based longitudinal study. Lipids Health Dis 19: 245. https://doi.org/10.1186/s12944-020-01419-z

**AUTHOR CONTRIBUTION:**

| Contribution | Suparmi S | Yuliyanti S | Karyadini HW | Syamsudin AMR | Gau EK |
|---|---|---|---|---|---|
| Concepts or ideas | x | | | | |
| Design | x | | | | |
| Definition of intellectual content | x | | | | |
| Literature search | x | x | x | x | x |
| Experimental studies | x | x | x | x | x |
| Data acquisition | x | | | x | x |
| Data analysis | x | x | x | | |
| Statistical analysis | x | x | x | | |
| Manuscript preparation | x | | | | |
| Manuscript editing | x | | | | |
| Manuscript review | x | x | x | x | x |

**Citation Format:** Suparmi S, Yuliyanti S, Karyadini HW, Syamsudin AMR, Gau EK (2024) Toxicity of sibutramine hydrochloride-adulterated weight loss supplements in rats based on biochemical and organ weight parameters. J Pharm Pharmacogn Res 12(2): 363–370. https://doi.org/10.56499/jppres23.1852_12.2.363