Open Acess
Jurnal Biota Vol. 10 No. 2 (2024) https://doi.org/10.19109/Biota.v10i2. 20109

Research Article

Safety Evaluation of Snake Plant (*Sansevieria trifasciata*) Leaves Extract as Potential Herbal Medicine

Laksmindra Fitria[1*], Isma Cahya Putri Gunawan[2], Wilda Bunga Tina Sanjaya[2]
[1] Laboratory of Animal Physiology, Department of Tropical Biology, Faculty of Biology, Universitas Gadjah Mada (UGM), Yogyakarta, Indonesia.
[2] Faculty of Biology, Universitas Gadjah Mada (UGM), Yogyakarta, Indonesia.
[*] Email: laksmindraf@ugm.ac.id

Received: 09/11/2023	Revised: 29/12/2023	Accepted: 08/01/2024

ABSTRACT
Snake Plant (Sansevieria trifasciata) has been commonly used as traditional herbal medicine in addition to being ornamental plant and phytoremediation agent. Toxicity studies on pharmaceutical substances are required to assess the level of hazard and safety before processing as drugs. Conventional toxicity test focused on determining LD50, despite the fact that not all substances induce death in experimental animals. They might survive but suffering or get sick. This study aimed to evaluate safety level of oral administration of chloroform extract of S. trifasciata leaves (CESTL) for 28 days (subacute) in Wistar rats (Rattus norvegicus) as model animal through the observation of clinical signs that lead to lethal and sublethal effects. The procedure referred to OECD Guideline No. 407 with the dose of CESTL was 1000 mg/kg bw (Limit Test). Adult female nulliparous Wistar rats were assigned into three groups which received CESTL, Tween 4 % (solvent for CESTL), or distilled water as control (placebo) 1 mL/individual/day. Parameters observed consisted of mortality, general physical examination, individual and social activity and behavior, body weight, body temperature, food intake, water consumption, fecal condition, and fasting blood glucose (FBG) level. Results showed that no animals died or suffered as a result of CESTL poisoning. There were no significant differences in all parameters value among three groups, indicating that CESTL did not generate adverse effects on animal normal physiological condition. Thus, it can be concluded that CESTL at the dose of 1000 mg/kg bw is relatively safe for consumption during subacute period.

Keywords: *Clinical signs; Drug discovery, OECD 407, Sansevieria trifasciata, Subacute toxicity.*

Introduction

Snake Plant (*Sansevieria trifasciata* Prain.) can be found in the wild, mainly in the tropics and subtropics regions, particularly in Africa, Australia, and Southeast Asia [1], [2]. This plant is easy to cultivate due to its ability to survive in a wide range of temperature and light, and can grow well at habitats from low to high altitudes. Habitat differences cause variations in the appearance of *S. trifasciata* [3], making them attractive as decorative plant [4], [5]. In addition to having lovely appearance and being easy to care, this plant helps to improve air quality by absorbing toxins and pollutants [6]. Ethnopharmacological studies reported that leaves of *S. trifasciata* (STL) have been utilized as traditional medicine to treat ear diseases, swelling, boils, fever, diarrhea, coughs, respiratory disorders, ulcers, snake bites, and hair loss [5], [7]. Preclinical

studies by [7] demonstrated that aqueous and ethanolic extracts of STL have analgesic and antipyretic activities. Aqueous extract of STL also has potential as antihyperglicemia or antidiabetic [8], [9]. Ethanolic extract of STL also has antiallergic and antianaphylactic properties [10]. Clinical trial by [4] showed that ointment containing ethanolic extract of STL has ability to cure patients with skin disease (corns) within 4 weeks. [5] reported that n-hexane, ethyl acetate, and methanolic extract of STL have antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*, whereas ethanolic extract of STL has antibacterial activity against *Pseudomonas aeruginosa* [11].

Phytochemical screening of chloroform extract of STL (CESTL) revealed several secondary metabolites such as alkaloids, flavonoids, stilbenoids, saponins, glycosides, terpenoids, tannins, proteins, carbohydrates, polyphenols, steroids [2], [11]. These phytoconstituents play a role as bioactive compounds in a variety of therapeutic properties such as antiinflammatory, antimicrobial, antioxidant, antiproliferative, cytotoxicity, etc. [2]. However, publication on medicinal properties of CESTL is very limited [12]. Regarding its function as a toxin-absorbing plant (phytoremediation agent) and rich of secondary metabolites, it is conceivable that CESTL is harmful when administered to subjects as part of medical treatment. Therefore, toxicity tests need to be carried out to anticipate negative effects on health. Preclinical toxicity testing from acute to chronic are the initial phase before exploring the potential therapeutic effects of CESTL. They provide a comprehensive investigation of safety and adverse effects, as well as dose-response for new drug development process [13]. This is due to the fact that herbal products require a longer period of time, regularity and consistency in consumption before revealing their potential as medicine.

Fitria *et al* [12], reported that single-dose acute oral toxicity study of CESTL at the dose of 2000 mg/kg bw has no observed adverse effect level (NOAEL). In the previous study, CESTL was only administered once and the duration of the trial was only 14 days. Traditional herbal medicine needs longer time to take effects as they work slowly than modern medicines [14]. Correct dose and appropriate duration of treatment are required as well as for particular disease, rather than unrestricted use. Herbal medicine is drug, therefore cannot be consumed freely like food. All effective drugs may produce adverse effects, herbal medicines are no exception [15]. Adverse effects of herbal medicines may result from their constituents, contaminants, inappropriate use, and inadequate safety data from basic research [14]. Therefore, it is suggested to continue the toxicity study of CESTL to the next step (subacute). This study aimed to investigate the toxicity signs that lead to lethal and sublethal effects of oral administration of CESTL given every day for 28 days (repeated-dose) in Wistar rats *Rattus norvegicus* Berkenhout 1769, as model animal following OECD Guideline No 407 OECD 2008.

Materials and methods

Plant Material and Extraction Method

Snake Plant leaves were collected from Bandar Lampung area, Province of Lampung, Indonesia. The species nomenclature *Sansevieria trifasciata Prain.* has been identified at Laboratory of Plant Systematics, Faculty of Biology UGM, validated with certificate No. 014526/S.Tb./II/2019, dated on February 25, 2019. The preparation of chloroform extract of *S. trifasciata* leaves (CESTL) followed maceration method by [11]. Leaves were washed with distilled water, finely chopped, and dried in oven at 50 °C until a constant dry weight was achieved. The dried material (simplicia) then was ground into powder, strained using 40 mesh sieve, and soaked in chloroform as solvent with a ratio of powder:chloroform = 1:3 (w/v) for 3×24 hours. The mixture was

shaken regularly every day to optimize the extraction, then filtered and evaporated using electric fan until completely dried. Stock of CESTL was stored in glass containers wrapped with aluminum foil and kept in the refrigerator 4 ℃ [12].

Animals

Fifteen female nulliparous Wistar rats (*Rattus norvegicus* Berkenhout, 1769) aged eight-week-old with body weight 174-285 g (mean= 244±26 g, median= 252 g) obtained from the breeding colony at the animal facility of Faculty of Biology UGM (Animal House) were used as experimental animals. Rats were housed in 38×25×23.5 cm^3 transparent polypropylene communal cages with metal wire mesh for the lid. Cage floor was covered with sterile wood shaving for bedding. Each cage was equipped with feeder and drinking bottle. Experiment was conducted at the animal room in Animal House with environmental parameters as follows: room temperature 26.4-28.7 ℃, relative humidity 65.5-82.2 %, illumination by artificial light from 7-watt LED bulb with standard photoperiod (12 hours light:12 hours dark). Air circulation was supported by air conditioner and exhaust fan. Cages were washed 2× per week with detergent and disinfectant. During the experiment, rats were fed with standard rodent chow (Ratbio®, P.T. Citra Ina Feedmill, Jakarta) and mineral water (P.T. Berkah Tirta Jaya, Yogyakarta) for drinking water. Animal care and husbandry referred to standard procedures for laboratory rats [16]. All procedures for the care and use of animals in this study was approved by the Research Ethics Commission of the Faculty of Veterinary Medicine UGM by the issuance of Ethical Clearance No: 00034/EC-FKH/Eks./2021, dated on April 12, 2021.

Experimental Design and Parameters

Rats were divided into three groups (n=5) which received CESTL, 4 % Tween80 (v/v), and distilled water as control/placebo. CESTL was dissolved in distilled water as the vehicle. Tween80 was used to make CESTL more soluble in water [12]. The procedure of the experiment referred to OECD Test Guideline No. 407 (OECD, 2008) with the dose of CESTL was 1000 mg/kg bw (Limit Test) as follows: CESTL, Tween80, or distilled water were administered orally using the gavage technique as much 1 mL/individual once every day in the afternoon (3-4 pm) for a consecutive 28 days. Parameters observed including the number of dead animals (mortality), sublethal effects and clinical manifestations that lead to illness, consisted of morphological or general physical examination, individual and social behavior and activities, food intake, drinking water consumption, and fecal condition. These parameters were recorded every day. Body weight, body temperature, and fasting blood glucose (FBG) level were measured on day 0, 7, 14, 21, and 28.

Data Analysis

Data were tabulated in Microsoft®Excel®v.2019 spreadsheet and continued with statistical analysis according to One-Way ANOVA and Duncan's Post Hoc Test (α= 0.05) using IBM®SPSS®v.25. Data were shown as description or visualized as line and bar charts.

Results and Discussion

Lethal and sublethal effects

Until the end of the experiment, no dead animals were found in all groups. However, survived animals during exposure to toxic compounds might experience physiological disturbances. Rats with health problems (including stress) can be identified by their general physical appearance as well as their individual and social behavior and activities. Provided checklist to observe clinical signs of pain and disease in rats [17]. During the experiment we did not find any clinical signs of pain and diseases following oral administration of CESTL Table 1.

As in single-dose toxicity study [12], no animals died in this repeated-dose toxicity study of CESTL. This result is consistent with toxicity studies of *S. trifasciata* aqueous extract [7], [8], ethanolic extract [7], [18], and methanolic extract [9]. According to [18], oral administration of *S. trifasciata* extract up to 18,000 mg/kg bw did not cause death in Wistar rats. It is suspected that *Sansevieria* is relatively safe as a medicinal ingredient. Toxicity studies of *S. liberica* methanolic extract [19], aqueous extract [20], and crude extract [21], [22], that also generated no mortality. The same result was found for ethanolic extract of *S. cylindrica* [23].

Table 1. Clinical signs of pain and disease in rats (OARS of Yale University, 2021)

Criteria	Control	Tween	Cestl
Abnormal posture (hunched)	-	-	-
More aggressive or unresponsive (placid) when handled	-	-	-
Decreased activity/mobility or hyperactive, including back-arching, belly-pressing, twitching, and staggering	-	-	-
Changes in facial expressions as measured by the Grimace Scale by NC3RS	-	-	-
Decreased body temperature (hypothermia)	-	-	-
Decreased food and drinking water consumption, which has an impact on weight loss	-	-	-
Less frequent in grooming resulting in scruffy and dull fur, piloerection	-	-	-
Decreased in nest-building, foraging, digging, and burrowing	-	-	-
Decreased response to external stimuli such as not avoiding when handled	-	-	-
Increased licking and scratching	-	-	-
Mucous membranes and extremities appear pale	-	-	-
Secretion of porphyrin (red pigment) around eyes, nose, and limbs	-	-	-
Separation from group or become solitary	-	-	-
Shallow and rapid breathing or gasping	-	-	-
Squinting eyes or closing eyes as if sleeping	-	-	-
Teeth chattering and vocalization	-	-	-

Food intake

Data of daily food intake and water consumption are key indications for determining the toxic effects of substances administered orally. Decreased food intake and water consumption refer to the presence of harmful materials within the body that cause animals to lose their appetite [24]. Results demonstrated a generally comparable trend in daily food intake in all groups figure 1 (A), as well as no significant differences were indicated in the average value among all groups figure 1 (B). Fecal examination showed normal condition. Xenobiotics that enter the body through oral route can disrupt the digestive system, with diarrhea being one of the most common symptoms [25]. Some mushy stools were found in all groups but only for a few days, therefore it did not interpret as diarrhea. As a result, we did not interpret this finding as diarrhea. According to [26], diarrhea is defined as frequent defecation in the form of liquid stool. The level of diarrhea (stool score or grading) is determined from the frequency of

defecation, stool form and consistency (wetness, stickiness, water content), presence of mucous, fats (steatorrhea) and/or blood (gross or occult blood) [25], [27]. This implies that various phytoconstituents in CESTL did not cause adverse effects on digestive system indicated by reduced appetite and diarrhea.

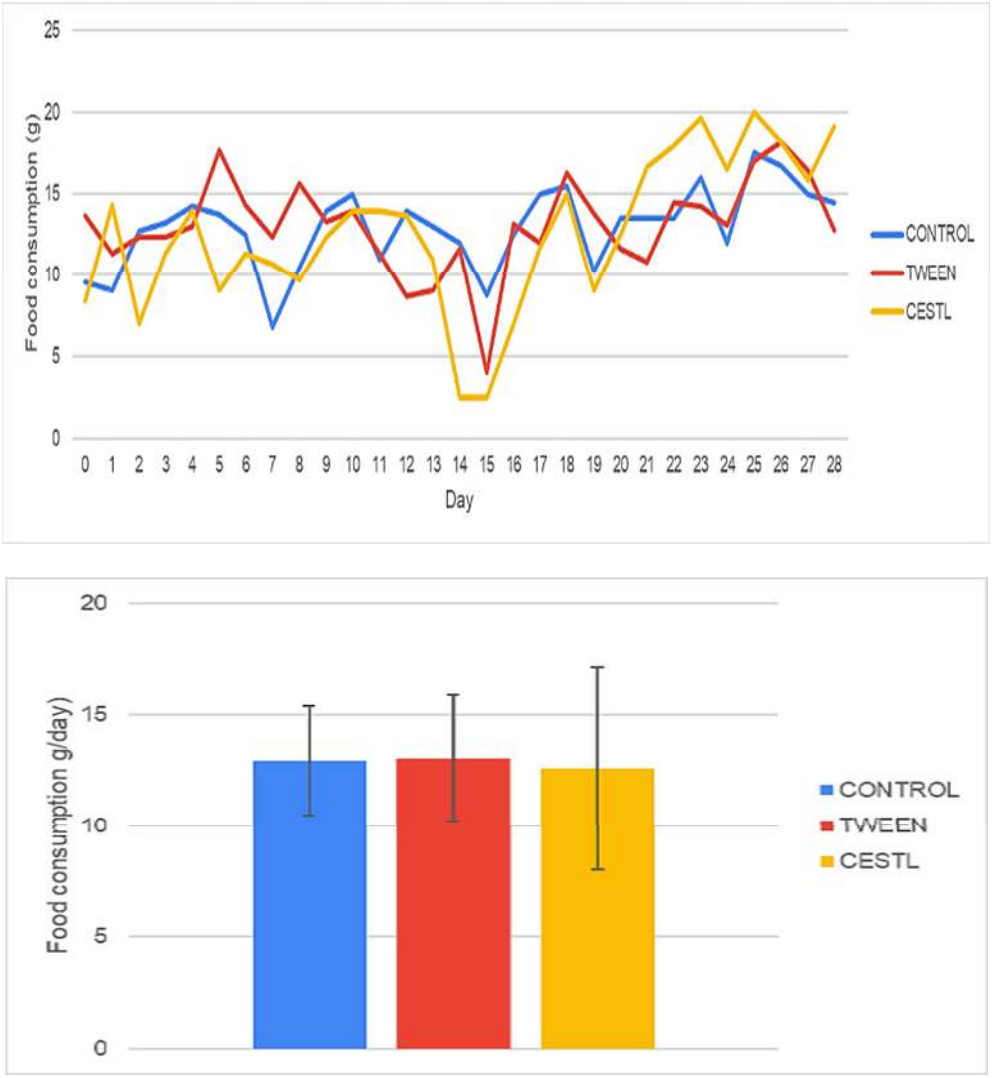


Figure 1. Food intake of rats during subacute oral administration of CESTL. (A) daily measurement; (B) average value.

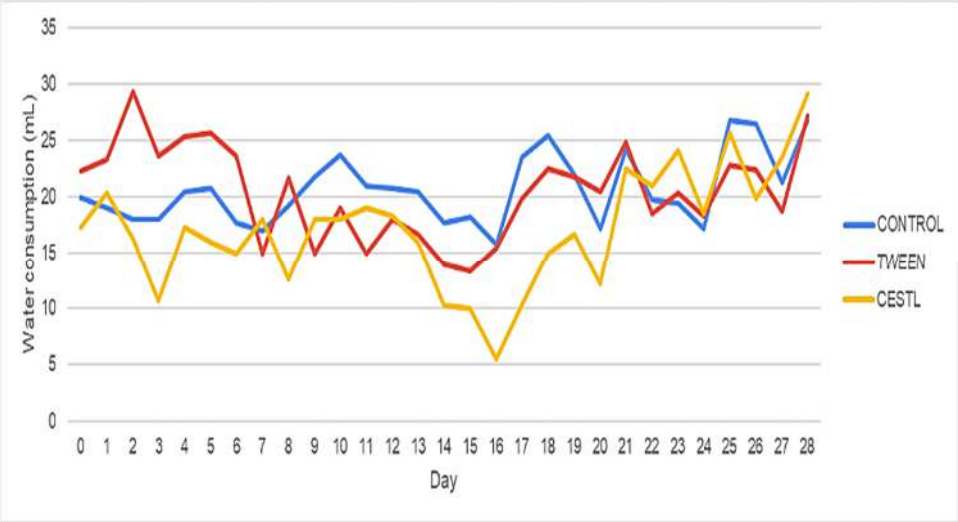
Ethnobotanical studies by [28] reported that *Sansevieria* leaves are commonly consumed by people in several African countries as food and traditional medicines, as well as feed for their livestock. For instance, *S. aethiopica* is used by people in Botswana to improve appetite in children. *S. hyacinthoides* is used by South Africans to treat digestive disorders, such as diarrhea, hemorrhoids, intestinal parasites, stomach problems, ulcers, and abdominal pains. *S. aethiopica* and *S. desertii* (synonim: *S. pearsonii*) are also applied for animal feed.

Reported that ethanolic extract of *S. trifasciata* exhibited antiulcer activity [18]. According to [29], secondary metabolites with antiulcer properties are mainly alkaloids, tannins, phenols and polyphenols (particularly flavonoids). Due to the

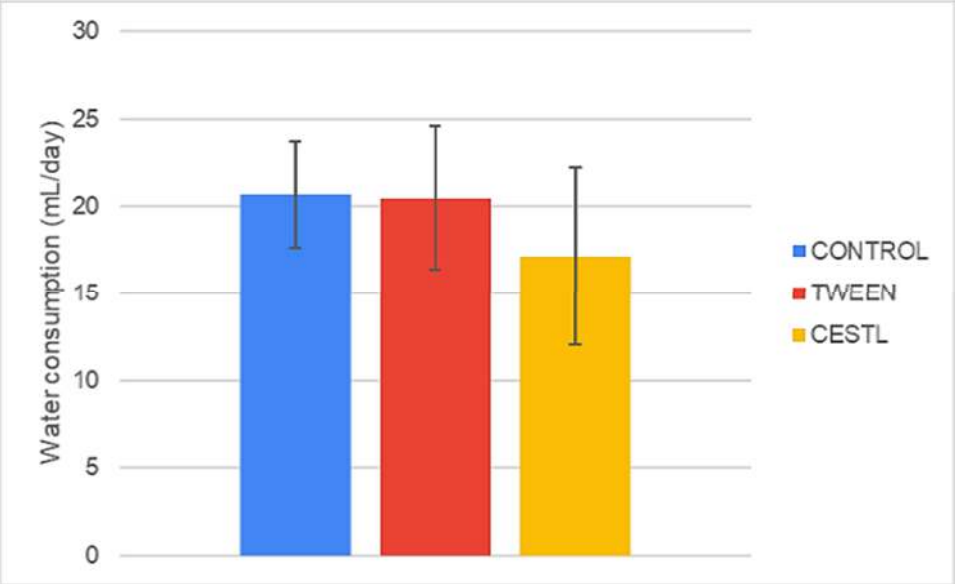
presence of these phytoconstituents in CESTL [2], [11], therefore, rather than being toxic to digestive system, CESTL has the potential as antiulcer or gastroprotective agent.

Drinking water consumption

The pattern of water consumption generally follows the food intake. Rats will drink after eating with a volume commensurate with the portion of the meal [30]. Alterations in food intake and water consumption are typically employed as indicators of the adverse effects of chemical substances [31]. Similar with food intake, results of daily water consumption during the experiment showed a relatively similar pattern in all groups figure 2 (A). The average value of water consumption of rats in CESTL group was slightly lower than in Control and Tween groups, however no significant differences were detected figure 2 (B). This demonstrated that CESTL has no negative impacts towards normal physiological condition.



A



B

Figure 2. Drinking water consumption of rats during subacute oral administration of CESTL. (A) daily measurement; (B) average value.

Body weight

Weight loss is one of the most noticeable sublethal effects, with the rate of weight loss increasing with type, dose, and duration of toxic substance exposure [32]. Weight loss during toxicity testing is a sign that the substance examined has a harmful effect [24]. During the experiment, body weight measurement showed a decline in all groups, with a generally similar trend figure 3 (A). Because animals body weight in each group varied from the start, weight reduction when compared among three groups was considerably significant figure 3 (B).

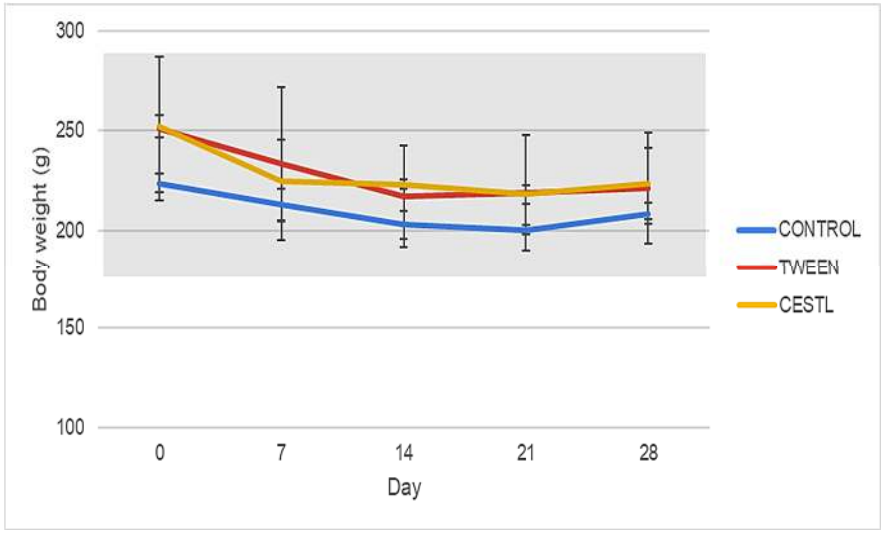
However, when calculated based on the initial and final body weight in each group, there is no significant difference. Significant weight loss is when the reduction exceeds 20 % of the initial body weight [33]. Control, Tween, and CESTL groups all had weight loss of 7, 12, and 11 %, respectively. According to mathematical analysis using second-order (quadratic) polynomials regression, the coefficient of weight reduction (R^2) in Control, Tween, and CESTL groups were 0.9714, 0.9785, and 0.9326, respectively (CESTL had the lowest rate). Nausea, emesis, diarrhea, and/or abdominal pain are some clinical signs which cause the animal losing appetite (hypophagia), and hence ends up with reduced body weight [34]. This finding showed that CESTL is safe since toxic substance that are taken orally usually cause severe weight loss as they profoundly interfere with the digestive system or gastrointestinal toxicity [24]. In addition, all animals final body weights were still within the baseline interval (174-285 grams), and no clinical signs were present, therefore it can be concluded that the weight reduction is not a clinical deterioration due to the toxic effect of CESTL.

Body temperature

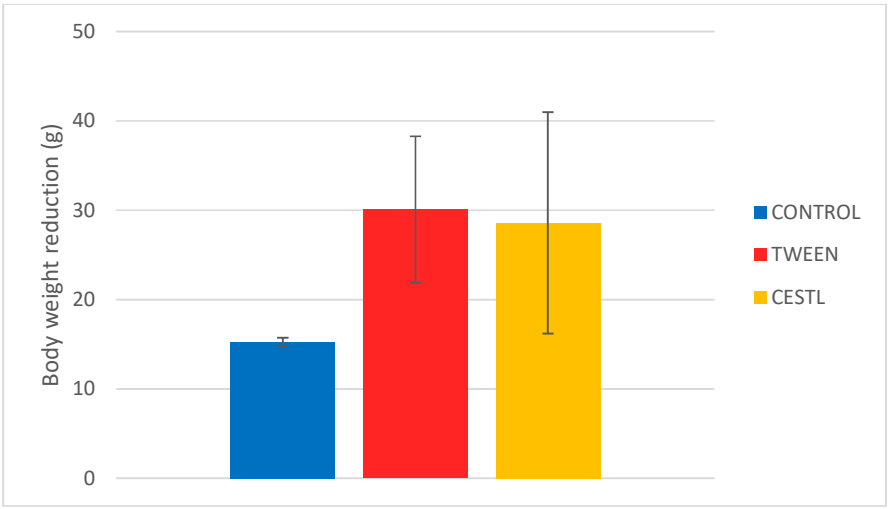
Understanding the changes of body temperature (thermoregulation) in response to the administration of toxic compounds including drugs is crucial because it affects physiological, behavioral, and pathological conditions. However, in toxicity studies, the dynamics of body temperature are still not given much consideration [35]. Acute exposure to hazardous chemical compounds (toxicants) induces a drop in body temperature (hypothermia) in rodents and other small mammals. This is because body heat is utilized to regulate multiple metabolisms in order to eliminate xenobiotics. [36] stated that lowering body temperature is an adaptive response to help recovering physiological conditions and improving survival following exposure to harmful substances, as well as protection against neurological injury [37]. In rodents, elevated body temperature (hyperthermia) is commonly associated with pathogenic infections and inflammatory reactions [35]. A chemical substance can induce fever because it contains constituents that are considered as antigenic, thus eliciting immune response. Fever can also occur due to xenobiotic interfering with prostaglandin synthesis through various proinflammatory mediators such as cytokines and tumor necrosis factor (TNF), which trigger the hypothalamus as thermoregulator to raise body temperature [38]. The measurement of body temperature during the experiment exhibited that body temperature of animals in all groups fluctuated in a relatively similar fashion figure 4. Statistical analysis confirmed that there were no significant differences among groups and time series. We found a slight variation in body temperature dynamics in Tween group in the last two weeks. All of the values, however, were within the baseline interval (33.9-36.1 °C). Therefore, it is possible to state that CESTL is safe to consume since it does not trigger fever or causing hypothermia.

According to [38], flavonoids also have antipyretic and antiinflammatory activities. Since CESTL also contains flavonoids [2], [11], thus oral administration of this substance may play a role in thermoregulation, causing CESTL

group to have body temperature dynamics that comparable to Control. This result is consistent with [7] that ethanolic extract of *S. trifasciata* leaves significantly has antipyretic and antiinflammatory properties due to the presence of flavonoids.



A



B

Figure 3. Body weight of rats during subacute oral administration of CESTL. (A) weekly measurement; (B) body weight reduction.

Fasting blood glucose (FBG) level

According to [39], FBG level significantly increases (hyperglycemia) following acute toxicity. Increasing FBG level also indicates stress in rats [40]. FBG levels measurement during the experiment showed that each group has a distinct pattern Figure 5. However, overall FBG level of all groups were within the baseline interval (112-237 mg/dL). Statistical analysis revealed no significant differences between groups and time series. Since there was no hyperglycemia episode (all animals were in normoglycemia), it can be concluded that CESTL does not generate adverse effect or induce stress. The pattern of FBG level in CESTL group indicated that the extract is safe to consume since it does not interfere with carbohydrate metabolism, particularly glucose metabolism. Disruption of glucose homeostasis causes an elevation in glucose

level (hyperglycemia) which initiates to several organs and tissues damages throughout the body. Furthermore, persistent hyperglycemia suppresses immunity and increases susceptibility to infection [41].

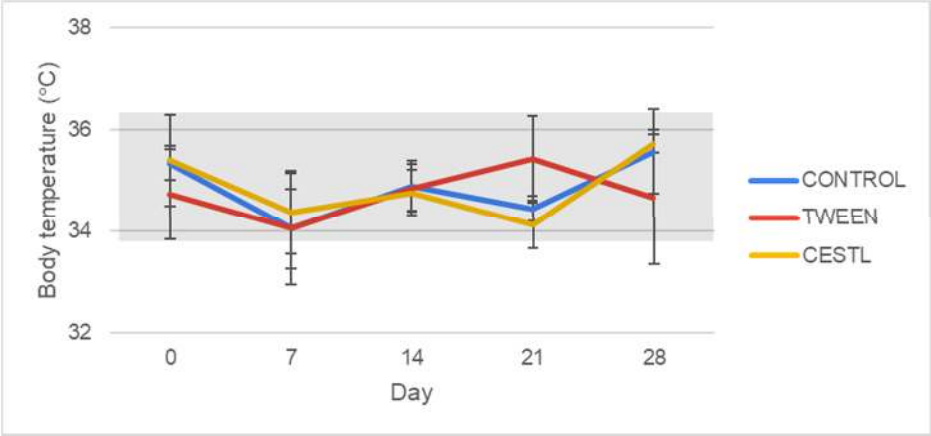


Figure 4. Body temperature of rats during subacute oral administration of CESTL (weekly measurement).

Reported that decoction of *S. trifasciata* leaves possesses hypoglicemic effect in diabetic rats due to the presence of polyphenols (flavonoids) and alkaloids [8]. Crude extract (aqueous) of *S. roxburghiana* was also able to reduce blood glucose levels in diabetic rats due to the high content of phenolic compounds [42]. Phytochemical study of CESTL by [2], [11] also exhibited the presence of flavonoids, phenols, and alkaloids. Therefore, rather than being toxic, CESTL possesses antidiabetic properties. However, before exploring the potential therapeutic effects of CESTL, a comprehensive investigation and subchronic to chronic toxicity studies should be conducted to provide data of safety and adverse effects, if any, of long-term consumption. This is due to the fact that, in general, herbal products require a longer period of time, regularity and consistency in consumption before revealing their potential as medicine [14], [15].

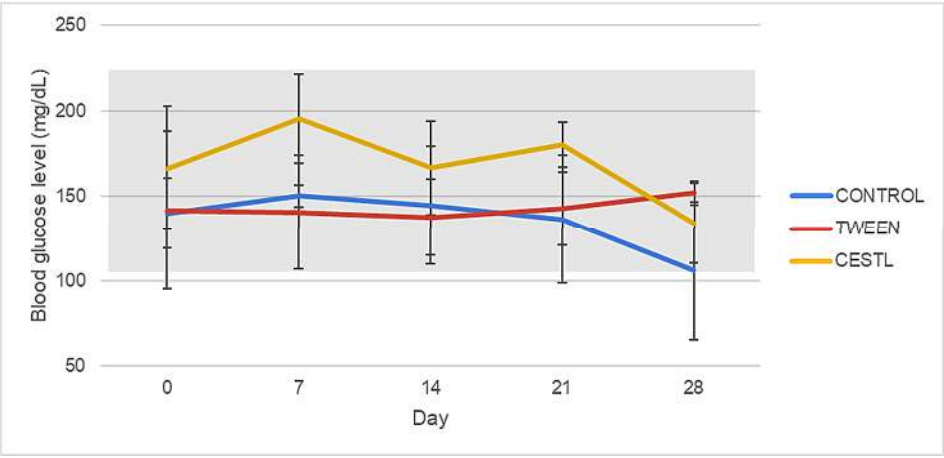


Figure 5. Blood glucose level of rats during subacute oral administration of CESTL (weekly measurement).

Conclusions

Chloroform extract of Snake Plant (*Sansevieria trifasciata* Prain.) leaves (CESTL) 1000 mg/kg bw is safe to be consumed every day (repeated-dose) during the subacute period (28 days) as there is no clinical symptoms of drug poisoning observed consisted of no mortality or sublethal effects, no signs of pain and diseases, normal food intake and water consumption. Body weight, body temperature and fasting blood glucose level are within normal range, indicated that CESTL does not interfere with normal physiological condition and health status. We schedule to conduct a similar experiment with male Wistar rats to obtain comprehensive information regarding the hazard and safety level of CESTL before exploring its potential as therapeutic agent.

Acknowledgments

This research was partially funded by "Hibah Kolaborasi Dosen dan Mahasiswa" (KDM) in Faculty of Biology UGM in the year 2021 (Grant Number: 1009/UN1/FBI/KSA/PT.01.03/2021, dated on March 25, 2021). Authors are grateful to the Head of Laboratory of Animal Physiology, Faculty of Biology UGM, and the Management of Animal House, Faculty of Biology UGM for making this research possible.

References

[1] S. S. Pinky, S. Monira, M. A. Hossain, and A. Hossain, "Antioxidant, Anti-inflammatory, Cytotoxic and Analgesic Activities of Sensevieria trifasciata," *Bangladesh Pharm. J.*, vol. 23, no. 2, pp. 195–200, 2020, doi: 10.3329/bpj.v23i2.48341.

[2] Z. M. Thu, K. K. Myo, H. T. Aung, C. Armijos, and G. Vidari, "Flavonoids and stilbenoids of the genera Dracaena and Sansevieria: Structures and bioactivities," *Molecules*, vol. 25, no. 11, p. 2608, 2020, doi: 10.3390/molecules25112608.

[3] A. R. P. Raharjeng, "Pengaruh faktor abiotik terhadap hubungan kekerabatan tanaman Sansevieria trifasciata L," *J. Biota*, vol. 1, no. 1, pp. 33–41, 2015, doi: 10.19109/Biota.v1i1.383.

[4] H. Afrasiabian, R. Hododi, M. H. Imanieh, and A. Salehi, "Therapeutic effects of Sansevieria trifasciata ointment in callosities of toes," *Glob. J. Health Sci.*, vol. 9, no. 2, pp. 265–268, 2017, doi: 10.5539/gjhs.v9n2p264.

[5] Y. Febriani, V. Mierza, N. P. Handayani, S. Surismayanti, and I. Ginting, "Antibacterial activity of lidah mertua (Sansevieria Trifasciata Prain.) leaves extract on Escherichia coli and Staphylococcus aureus," *Open Access Maced. J. Med. Sci.*, vol. 7, no. 22, p. 3882, 2019, doi:10.3889%2Foamjms.2019.525.

[6] R. Nuraeni and S. Windyariani, "Effectiveness of Sansavieria trifasciata Extract Bracelet in Absorbing Carbon Monoxide (Co) in Cigarette Smoke," *J. Biota*, vol. 5, no. 2, pp. 96–103, 2019, doi: 10.19109/Biota.v5i2.3336.

[7] J. A. Sunilson, P. Jayaraj, R. Varatharajan, J. Thomas, J. James, and M. Muthappan, "Analgesic and antipyretic effects of Sansevieria trifasciata leaves," *African J. Tradit. Complement. Altern. Med.*, vol. 6, no. 4, 2009, https://pubmed.ncbi.nlm.nih.gov/20606773.

[8] N. Qomariyah, "Antidiabetic effects trifasciata in alloxan," *ITB Sci*, vol. 44, pp. 308–316, 2012, doi: 10.5614/itbj.sci.2012.44.4.2.

[9] B. Dey, R. Bhattacharjee, A. Mitra, R. K. Singla, and A. Pal, "Mechanistic explorations of antidiabetic potentials of Sansevieria trifasciata," *Indo Glob. J. Pharm. Sci.*, vol. 4, no. 2, pp. 113–122, 2014, doi: 10.35652/IGJPS.2014.115.

[10] R. N. Andhare, M. K. Raut, and S. R. Naik, "Evaluation of antiallergic and

anti-anaphylactic activity of ethanolic extract of Sanseveiria trifasciata leaves (EEST) in rodents," *J. Ethnopharmacol.*, vol. 142, no. 3, pp. 627–633, 2012, doi: 10.1016/j.jep.2012.05.007.

[11] W. Dewatisari, L. H. Nugroho, E. Retnaningrum, and Y. A. Purwestri, "The potency of Sansevieria trifasciata and S. cylindrica leaves extracts as an antibacterial against Pseudomonas aeruginosa," *Biodiversitas J. Biol. Divers.*, vol. 22, no. 1, 2021, doi: 10.13057/biodiv/d220150.

[12] L. Fitria, I. C. P. Gunawan, W. B. T. Sanjaya, and M. I. Meidianing, "Single-dose acute oral toxicity study of chloroform extract of snake plant (Sansevieria trifasciata Prain.) leaf in Wistar rats (Rattus norvegicus Berkenhout, 1769)," *J. Trop. Biodivers. Biotechnol.*, vol. 7, no. 1, p. 69389, 2022, doi: 10.22146/jtbb.69389.

[13] S. Parasuraman, "Toxicological screening," *J. Pharmacol. Pharmacother.*, vol. 2, no. 2, p. 74, 2011, doi: 10.4103/0976-500x.81895.

[14] R. Kasole, H. D. Martin, and J. Kimiywe, "Traditional medicine and its role in the management of diabetes mellitus:"patients' and herbalists' perspectives"," *Evidence-Based Complement. Altern. Med.*, vol. 2019, doi: 10.1155/2019/2835691.

[15] J. Zhang, I. J. Onakpoya, P. Posadzki, and M. Eddouks, "The safety of herbal medicine: from prejudice to evidence," *Evidence-based complementary and alternative medicine*, vol. 2015. Hindawi, 2015, doi: 10.1155/2015/316706.

[16] K. Bayne, *Revised Guide for the Care and Use of Laboratory Animals available. American Physiological Society.*, vol. 39, no. 4. 1996.

[17] O. of A. R. S. (OARS) of Y. University, "Clinical Signs of Pain and Disease in Laboratory Animals," 2021. https://your.yale.edu/policies-procedures/guides/4446-clinical-signs-pain-and-disease-laboratory-animals

[18] O. M. Ighodaro, A. M. Adeosun, B. F. Ojiko, A. T. Akorede, and O. Fuyi-Williams, "Toxicity status and antiulcerative potential of Sansevieria trifasciata leaf extract in Wistar rats," *J. Intercult. Ethnopharmacol.*, vol. 6, no. 2, p. 234, 2017, doi: 10.5455%2Fjice.20170421103553.

[19] I. C. Orabueze, S. C. Uzor, B. Ndiaye, D. Uba, D. A. Ota, and J. Agbedahusi, "Antimalarial, Antioxidant Activities and Chemoprofile of Sansevieria liberica Gerome and Labroy (Agavaceae) Leaf Extract," *Adv. Pharmacol. Pharm. Sci.*, vol. 2021, doi: 10.1155/2021/9053262.

[20] N. K. Achi and O. C. Ohaeri, "Acute and subacute toxicity studies of Sansevieria liberica aqueous leaf extracts.," 2012.

[21] E. C. Chinasa, I.-A. S. Ifeoma, E. C. Obodoike, and E. S. Chhukwuemeka, "Evaluation of anti-inflammatory property of the leaves of S*ansevieria liberica* ger. and labr.(fam: Dracaenaceae)," *Asian Pac. J. Trop. Med.*, vol. 4, no. 10, pp. 791–795, 2011, doi: 10.1016/s1995-7645(11)60195-8.

[22] A. P. Akah, T. S. Nwagu, and M. N. Oforkansi, "Evaluation of the anti-snake venom activity of leaf extract of S*ansevieria liberica* ger. & labr (Agavaceae.) in mice," *Int J Sci*, vol. 8, pp. 60–68, 2019, doi: 10.18483/ijSci.2012.

[23] S. Shewale *et al.*, "Evaluation and assessment of the acute toxic potential of Sansevieria cylindrica and Plumeria obtusa plant extracts in wistar albino rats," *J. Nat. Remedies*, pp. 209–220, 2022, doi: 10.18311/jnr/2022/28768.

[24] M. Todić, S. Bakić, B. Begović, S. Krošnjar, and I. Zulić, "Food and water consumption in assessment of

acute oral toxicity of HEPALIP FORTE in rats," *Biomol. Biomed.*, vol. 3, no. 4, pp. 47–53, 2003, doi: 10.17305/bjbms.2003.3493.

[25] V. Escudero-Vilaplana *et al.*, "Assessment of diarrhea as side effect of oral targeted antineoplastic agents in clinical practice," *Support. Care Cancer*, vol. 29, pp. 4673–4681, 2021, doi: 10.1007/s00520-021-06016-z.

[26] D.-M. Su, J.-B. Long, X.-P. Liu, and S.-B. Li, "Anti-diarrhea effects of polysaccharides from Zingiber officinale rhizome on a rat diarrhea model," *Trop. J. Pharm. Res.*, vol. 17, no. 10, pp. 1999–2005, 2018, doi: 10.4314/tjpr.v17i10.15.

[27] S. K. Yim, S. W. Kim, and S. T. Lee, "Efficient stool collection methods for evaluating the diarrhea score in mouse diarrhea models," *In Vivo (Brooklyn).*, vol. 35, no. 4, pp. 2115–2125, 2021, doi: 10.21873/invivo.12481.

[28] R. T. Nyenya and B. Stedje, "Ethnobotanical studies in the genus Sansevieria Thunb.(Asparagaceae) in Zimbabwe.," *Ethnobot. Res. Appl.*, vol. 9, pp. 421–443, 2011.

[29] M. Sharifi-Rad *et al.*, "Antiulcer agents: From plant extracts to phytochemicals in healing promotion," *Molecules*, vol. 23, no. 7, p. 1751, 2018, doi: 10.3390%2Fmolecules23071751.

[30] K. S. Laaksonen, T. O. Nevalainen, K. Haasio, I. H. E. Kasanen, P. A. Nieminen, and H. M. Voipio, "Food and water intake, growth, and adiposity of Sprague-Dawley rats with diet board for 24 months," *Lab. Anim.*, vol. 47, no. 4, pp. 245–256, 2013, doi: 10.1177/0023677213488103.

[31] Y.-L. Zhao *et al.*, "Acute and chronic toxicity of indole alkaloids from leaves of Alstonia scholaris (L.) R. Br. In mice and rats," *Nat. Products Bioprospect.*, vol. 10, pp. 77–88, 2020, doi: 10.1007/s13659-020-00237-1.

[32] M. Wang *et al.*, "Relationship between magnitude of body weight effects and exposure duration in mammalian toxicology studies and implications for ecotoxicological risk assessment," *Environ. Sci. Eur.*, vol. 31, pp. 1–7, 2019, doi: 10.1186/s12302-019-0221-1.

[33] S. R. Talbot *et al.*, "Defining body-weight reduction as a humane endpoint: a critical appraisal," *Lab. Anim.*, vol. 54, no. 1, pp. 99–110, 2020, doi: 10.1177/0023677219883319.

[34] H. Gelberg, "Pathophysiological mechanisms of gastrointestinal toxicity," *Compr. Toxicol.*, p. 139, 2018, doi: 10.1016%2FB978-0-12-801238-3.10923-7.

[35] C. J. Gordon, "Response of the thermoregulatory system to toxic insults," *Front Biosci (Elite Ed)*, vol. 2, pp. 293–311, 2010, doi: 10.2741/e91.

[36] C. J. Gordon, P. J. Spencer, J. Hotchkiss, D. B. Miller, P. M. Hinderliter, and J. Pauluhn, "Thermoregulation and its influence on toxicity assessment," *Toxicology*, vol. 244, no. 2–3, pp. 87–97, 2008, doi: 10.1016/j.tox.2007.10.030.

[37] S. M. Vučković *et al.*, "Synergistic interaction between ketamine and magnesium in lowering body temperature in rats," *Physiol. Behav.*, vol. 127, pp. 45–53, 2014, doi: 10.1016/j.physbeh.2014.01.006.

[38] G. A. R. A. Jaleel, H. M. I. Abdallah, and N. E. L. S. Gomaa, "Pharmacological effects of ethanol extract of Egyptian Artemisia herba-alba in rats and mice," *Asian Pac. J. Trop. Biomed.*, vol. 6, no. 1, pp. 44–49, 2016, doi: 10.1016/j.apjtb.2015.10.005.

[39] A. M. Sabzghabaee, N. Eizadi-Mood, F. Gheshlaghi, N. Adib, and L. Safaeian, "Is there a relationship

between admission blood glucose level following acute poisoning and clinical outcome?," *Arch. Med. Sci.*, vol. 7, no. 1, pp. 81–86, 2011, doi: 10.5114%2Faoms.2011.20608.

[40] A. O. Morakinyo *et al.*, "Adverse effects of noise stress on glucose homeostasis and insulin resistance in Sprague-Dawley rats," *Heliyon*, vol. 5, no. 12, 2019, doi: 10.1016%2Fj.heliyon.2019.e03004.

[41] S. Kawahito, H. Kitahata, and S. Oshita, "Problems associated with glucose toxicity: role of hyperglycemia-induced oxidative stress," *World J. Gastroenterol. WJG*, vol. 15, no. 33, p. 4137, 2009, doi: 10.3748%2Fwjg.15.4137.

[42] N. Bhattacharjee *et al.*, "Sansevieria roxburghiana Schult. & Schult. F.(Family: Asparagaceae) attenuates type 2 diabetes and its associated cardiomyopathy," *PLoS One*, vol. 11, no. 11, p. e0167131, 2016, doi: 10.1371/journal.pone.0167131.