Global Medical and Health Communication

Online submission: https://ejournal.unisba.ac.id/index.php/gmhc
DOI: https://doi.org/10.29313/gmhc.v10i3.9662

GMHC. 2022;10(3):183–189
pISSN 2301-9123 | eISSN 2460-5441

RESEARCH ARTICLE

Histopathology of Nephrotoxicity Associated with Administered Water Extract Purple Sweet Potato (*Ipomoea batatas*) in Mice (*Mus musculus*) in Stratified Phases of Dose

Meta Maulida Damayanti,[1] Raden Anita Indriyanti,[2] Yuktiana Kharisma,[1] Yuke Andriane,[2] Uci Ari Lantika,[3] Ratna Damailia,[4] Meike Rachmawati[1]

[1]Department of Pathology Anatomy, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,
[2]Department of Pharmacology, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,
[3]Department of Biomedical Medic, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,
[4]Department of Microbiology, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia

Abstract

The main aim of the registered purple sweet potato (*Ipomoea batatas*) is to provide minimize the adverse chemical drugs, in addition to its anti-inflammatory, antioxidant, and antimicrobial effects. Potentially adverse effects may be observed in laboratory animals in particular, the extent to which this administration can cause toxicity. This study aimed to examine the histopathology of nephrotoxicity associated with administered water extracts of purple sweet potato in mice with stratified doses. The study was conducted at the Biomedical Laboratory, Faculty of Medicine, Universitas Islam Bandung on September 2019. Female mice (*Mus musculus*) strain Swiss Webster, aged between 6–8 weeks weighing 25 to 30 g, were obtained from Biopharma Laboratory, Bandung. The animal was acclimatized for seven days before being administered water extract purple sweet potato: eleven mice, one control group, and ten treatment groups underwent toxicity doses of purple sweet potato water extract administration. Purple sweet potato variant of Ayamurasaki prepared in various oral doses. The results show in the control group there were no histopathological changes, but in the group administered water extract purple sweet potato from the first phase seems in a mild grade of macrophage accumulation, mild vacuolization of tubular epithelial cells, mild vascular dilatation, and mild hydrophilic degeneration. In the second phase, macrophage accumulation was visible in moderate grades. The LD50 of purple sweet potato extract is greater than 5,000 mg/kgBW. The findings of this study indicate that registration of purple sweet potato extract in confirmatory doses is safe to administer and did not exhibit any mortality. The toxicity test of purple sweet potato water extracts in the kidney exhibits minimal chemical effects.

Keywords: Extract purple sweet potato, histopathology of kidney, nephrotoxicity

Introduction

The kidneys are responsible for maintaining the body's internal environment's homeostasis, which includes water, electrolyte, nitrogen, and acid-base balances. The kidney is commonly involved in the negative consequences of exogenous chemicals, such as medications. The use of drugs in therapy has the potential to induce direct toxicity. Despite this, drug-induced nephrotoxicity has been linked to substantial side effects, with antimicrobials accounting for one-third of the cases.[1] Proving the role of causation in drug-induced kidney disease is complex because it necessitates an understanding of the drug's biological relevance, mechanism of injury, duration, and evaluation of competing risk factors. These phenotypes provide a standardized framework for doctors, researchers, industry, and regulatory authorities to evaluate medication nephrotoxicity in a variety of situations.[2] To eliminate the side effects of utilizing medications, natural components, or medicinal plants can be used to decrease negative responses that can lead to kidney disorder. Medicinal plants are often better tolerated than synthetic drugs, according to a review of clinical data on adverse effects. However, major adverse effects, such as herbal-drug combinations, should be taken into account.[3]

Medicinal plants have been used in various countries for years and have contributed significantly to the treatment system,[4] particularly in Indonesia. Plants with medicinal characteristics are useful in herbal therapies and can be used to treat a variety of disorders

Received: 24 May 2022; Revised: 17 August 2022; Accepted: 17 August 2022; Published: 20 August 2022

Correspondence: Meta Maulida Damayanti, drg., M.Kes. Department of Pathology Anatomy, Faculty of Medicine, Universitas Islam Bandung. Jln. Tamansari No. 22, Bandung 40116, West Java, Indonesia. E-mail: meta-md@unisba.ac.id

due to phytoconstituents. Phytochemicals are natural chemical components found in variable concentrations in plant sections (leaves, trunks, and roots) that act as disease defense mechanisms. Purple sweet potatoes, scientifically known as *Ipomoea batatas* L., were one of the first plants utilized by traditional healers to treat a range of diseases.[5]

Ipomoea batatas L., contain a high concentration of carbs, fiber, vitamins, and minerals, also flavonoid and phenolic compound.[6,7] Four anthocyanins derived from peonidin and three anthocyanins derived from cyanidin were found to contribute significantly to antioxidant activity.[8] Biological activities of ipomoea consist of anticancer, anti-diabetic, anti-inflammatory, antibacterial, and hepatoprotective abilities.[9]

In the evolution of the existing therapeutic system, the perspective of ethnopharmacological research, and drug development from natural sources have played a significant role. Medicinal plant ethnopharmacology needs to be studied more thoroughly before it can be used as a treatment. The majority of natural sources with active chemicals employed today have ethnomedical applications. Ethnopharmacology expertise can be valuable to discover and create new ideas, safe, and economical medications.[10]

The ability to identify these effects early on is critical for allowing novel, safe medications to enter the market. Acute toxicity is defined as an unwanted consequence that occurs immediately or within a certain period after single or multiple doses of the chemical within 24 hours. Toxicity tests, on the other hand, are required to determine the efficacy of natural treatments. This study was to evaluate the histopathology of nephrotoxicity-associated administered water extracts of purple sweet potato in mice with stratified doses.

Methods

The purple sweet potato (*Ipomoea batatas*) variant of Ayamurasaki has gone through a plant determination process at the Herbarium Laboratory of a School of Life Science and Technology, Institut Teknologi Bandung last 2018 (2839/II.CO2.2/PL/2018). Purple sweet potato water extraction using cold maceration method in aqua dest for 48 hours, filtered and evaporated. This aqueous extract is then prepared in various oral doses.[11,12]

Female mice (*Mus musculus*) strain Swiss Webster, aged between 6–8 weeks weighing 25 to 30 g, were obtained from Biopharma Laboratory, Bandung. The study was conducted at the Biomedical Laboratory, Faculty of Medicine, Universitas Islam Bandung on September 2019. The animal was acclimatized for seven days before being administered water extract sweet potato: eleven mice, one control group, and ten treatment groups that underwent toxicity dose of purple sweet potato water extract administration. This method was following the used by Chinedu et al.[13] Animal models were separated into three phases and one confirmation phase, with the results of each phase determining the next step to be taken (i.e., whether to end the process or move on to the next step). The first stage consists of four mice, which are separated into four groups of one animal each. In stage two, three mice are divided into three groups of one animal each. Stage three also involves three mice, which must be divided into three groups of one animal each. Each group in each step gave varying doses of the test material to the various animals. The animals should be evaluated for 1 hour after administration, Then, for the next 24 hours, 10 minutes every 2 hours. Toxicity-related behavioral signs and mortality should be recorded. If no mortality is detected at this phase, research testing should proceed to the next. The final stage is the confirmatory stage, in which if mortality was observed at a given dose in any of the previous stages, To ensure that the substrate material was the cause of such deaths, a confirmatory test should be undertaken.

The doses of each group of phases are documented in Table 1. Histopathological assessments by kidney biopsy were previously anesthetized using 10 mg/kg body weight of ketamine given intramuscularly. The paraffin-embedded fixed kidney tissue was dehydrated in successive grades of ethanol. Hematoxylin-eosin (HE) staining was used on kidney tissue blocks cut into 4-µm sections. Macrophage accumulation, vacuolization of tubular epithelial cells, vascular dilatation, and hydrophilic degeneration were graded as follows: no damage (– or 0), mild (± or 1, unicellular, patchy isolated damage), moderate (+ or 2, damage <25%), severe (++ or 3, damage 25% to 50%), and very severe (+++ or 4, damage >50%).[14] The histopathological analyses were performed by a pathologist. The data were analyzed using Microsoft 365.

To minimize animal suffering, all experimental procedures involving animals were carried out by

Table 1 Doses of Each Group of Stages in This Study

Phase	Dose (mg/kgBW)			
	Group 1	Group 2	Group 3	Group 4
1	50	200	400	800
2	1,000	1,500	2,000	
3	3,000	4,000	5,000	

Note: LD50=maximum dose of no mortality+minimum dose of mortality/2

the ARRIVE guidelines 2.0 for the care and use of laboratory animals.[15] This study was approved by the Health Research Ethics Committee of the Universitas Islam Bandung with Ethical Approval Number: 110/KEPK-Unisba/XI/2020.

Results

In the control group there were differences in macrophage accumulation, tubular epithelial cell vacuolization, vascular dilatation, and hydrophilic degeneration with the treatment group at the start of the first phase (Table 2). However, at the start of the second phase, macrophage accumulation was visible in moderate grades (Table 3). These indicates whether or not there is acute kidney injury. The histological examination revealed no differences in tissue damage between the right and left kidneys (Table 2, Table 3, and Table 4).

Kidney histopathology shown in the control group showed normal renal cortex, relatively healthy glomerulus, no accumulation of macrophages, dilated blood vessels, epithelial vacuolization, and degeneration. The treatment group showed histologic changes. Changes in kidney structure in the form of accumulation of macrophages range from mild to moderate grades. Macrophage accumulation with a positive value of 2/moderate was found starting at the beginning of the second phase of the treatment group (Figure). Necrotic conditions were not found in all control and treatment groups.

Discussion

This preclinical study provides continued evidence that nephrotoxicity is caused by the high dose of water extract purple sweet potato (*Ipomoea batatas*). Importantly in our model, in the confirmatory phase, 5,000 mg/kg body

Table 2 Histopathological Grade Change in the First Phase

Histopathological Changes	C S/D	50 S/D	200 S/D	400 S/D	800 S/D
Macrophage accumulation	−/−	+/+	+/+	+/+	+/+
Vacuolization of tubular epithelial cells	−/−	+/+	+/+	+/+	+/+
Vascular dilatation	−/−	+/+	+/+	+/+	+/+
Hydrophilic degeneration	−/−	+/+	+/+	+/+	+/+

Note: S: sinistra; D: dextra; no damage (– or 0), mild (± or 1, unicellular, patchy isolated damage), moderate (+ or 2, damage <25%), severe (++ or 3, damage 25% to 50%), and very severe (+++ or 4, damage >50%). severe (++ or 3, damage between 25 and 50%), and very severe (+++ or 4, damage >50%)

Table 3 Histopathological Grade Change in the Second Phase

Histopathological Changes	1,000 S/D	1,500 S/D	2,000 S/D
Macrophage accumulation	++/++	++/++	++/++
Vacuolization of tubular epithelial cells	+/+	+/+	+/+
Vascular dilatation	+/+	+/+	+/+
Hydrophilic degeneration	+/+	+/+	+/+

Note: S: sinistra; D: dextra; no damage (– or 0), mild (± or 1, unicellular, patchy isolated damage), moderate (+ or 2, damage <25%), severe (++ or 3, damage 25% to 50%), and very severe (+++ or 4, damage >50%). severe (++ or 3, damage between 25 and 50%), and very severe (+++ or 4, damage >50%)

Table 4 Histopathological Grade Change in the Third Phase

Histopathological Changes	3,000 S/D	4,000 S/D	5,000 S/D
Macrophage accumulation	++/++	++/++	++/++
Vacuolization of tubular epithelial cells	+/++	+/+	+/+
Vascular dilatation	+/+	+/+	+/+
Hydrophilic degeneration	+/+	+/+	+/+

Note: S: sinistra; D: dextra; no damage (– or 0), mild (± or 1, unicellular, patchy isolated damage), moderate (+ or 2, damage <25%), severe (++ or 3, damage 25% to 50%), and very severe (+++ or 4, damage >50%). severe (++ or 3, damage between 25 and 50%), and very severe (+++ or 4, damage >50%)

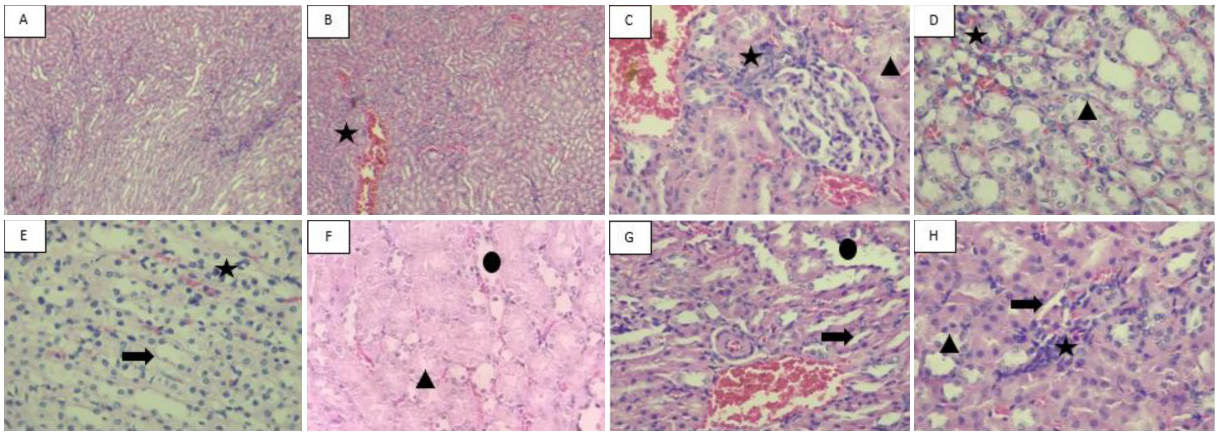

Figure Histopathology of Kidney

Light micrographs of the kidney sections based on histopathological changes among a group with HE staining. (**A**) Control group (100×). (**B**) The initial first phase (100×). (**C**) The last first phase (400×). (**D**, **E**) The second phase (400×). (**F**, **G**) The initial third phase (400×); (**H**) The last third phase (400×). The star (★) macrophage accumulation, the triangle (▲) vacuolization of tubular epithelial cells, the arrow (➡) vascular dilatation, and the circle (●) hydrophilic degeneration

weight no mortality occurs. Purple sweet potato has a high anthocyanin content compared to other sweet potato variants. Purple sweet potato contains several phytochemical substances such as saponins, alkaloids, flavonoids, tannins, triterpenoids, and quinones which are proven to have various benefits and are widely used. However, its absorption into the systemic circulation may cause toxicity. The toxicity of purple sweet potato is generally indicated by an increase in the accumulation of macrophages to necrosis.

The results of the study and histopathological observations of mice's kidneys after being given purple sweet potato with 3 phases dose of toxicity test showed that there was an accumulation of macrophage in mild to moderate in all treatment groups. Giving a dose of 50 started to cause mild macrophage accumulation, vacuolization of tubular epithelial cells, vascular dilatation, and hydrophilic degeneration. This occurs due to toxic doses of purple sweet potato that accumulate in the kidneys, causing tubular epithelial cells and capillary endothelial cells to undergo oxidative injury from excessive reactive oxygen species (ROS) formation so that tubular epithelial cells are damaged and become inflamed. Histopathological changes involve complex interactions between Kidney hemodynamics, tubular and endothelial cell damage, and the inflammatory process are all factors to consider. There is increasing evidence supporting the role of impaired kidney vascular function, especially at the microvascular level, in the initiation and progression of early tubular damage. Cell injury and vascular endothelial cell dysfunction play important roles in this phase of the toxicity test. Endothelial cells lose their ability to

control systemic vascular resistance, perfusion, permeability, inflammation, and adhesion. The loss of this regulating function has a negative impact on kidney function.[16,17]

Research conducted by Kim et al.[18] looked at the effect of giving povidone-iodine which is widely used as an antiseptic on toxicity which was seen in the microscopic picture of the kidney showing tubular atrophy, various casts (erythrocytes, leukocytes, and epithelial cell casts) in the distal tubule, and inflammatory cell infiltration in the interstitium. The administration of purple sweet potato supplementation in Wistar rats induced by gentamicin showed more regeneration of kidney tubular epithelial cells than Wistar rats without purple sweet potato extract supplementation.

Purple sweet potato is good to be consumed as an alternative therapy because it has many beneficial phytopharmaceuticals from the safe dosage. Anthocyanin purple sweet potato (APSP) contains antioxidant and anti-apoptotic properties, as well as the ability to regulate the c-Jun N-terminal kinase (JNK) signaling pathway, making it a potential treatment for reducing lead (Pb)-caused reproductive damage.[19] *Ipomoea batatas* have been shown to protect the liver from alcohol-induced hepatotoxicity and fatty liver disease.[20] Sweet potato root extracts contain anthocyanins and flavonoids, which have anticancer potential against breast cancer cell lines.[21] Research on the consumption of sweet potatoes has been done quite a lot and the results are good. In rats fed a high-cholesterol diet, a combination of purple sweet potato tuber water extract and honey can keep lipid profiles and MDA in the normal range.[22] Medicinal plants can induce kidney injury by causing mild interstitial inflammation with vascular congestion, moderate inflammation, vascular congestion, and severe inflammation and vascular congestion.[23] Deoxycorticosterone acetate (DOCA-salt) was combined with purple sweet potato extract ethanol (EP) to repair kidney injury, decrease smooth muscle cell proliferation, and reduce aorta wall thickening.[24]

In this study, giving a dose of 5,000 mg/kgBW can lead to nephrotoxicity or mild acute kidney injury (AKI, based on the histopathological description, it is not moderate or severe. Because the condition of the battery is heavy and medium. According to several studies, animals model with moderate and severe AKI experience transitory unilateral ischemia, which results in histologic alterations and kidney destruction within both the mild and severe AKI groups that received four weeks of treatment. After severe ischemia, acute tubular damage with casts and loss of brush boundaries of the tubular epithelium was substantially more evident than after moderate ischemia, with the corticomedullary junction being the most conspicuous. The cortex showed early shrinkage of single nephrons, as well as perivascular and interstitial inflammatory cell infiltration.[25]

Induction of purple sweet potato caused histopathological changes, starting from the accumulation of macrophage, vacuolization of tubular epithelial cells vascular dilatation hydrophilic degeneration even at a dose of 5,000 mg/kgBW, the changes that occur are mild, even at the beginning of the administration of a light dose, the changes are considered non-existent.

The administration of *Ipomoea batatas* can induce mild AKI, and it may become moderate or even severe with doses of more than 5,000 mg/kgBW. This is in line with research conducted by Won et al.[26] on the administration of cisplatin. After a single cisplatin treatment, the kidney showed morphological alterations, including significant inflammation and degradation in the proximal and distal tubules. The morphological alterations, on the other hand, were typically thought to be minor or non-existent. On day 3, cisplatin-induced kidney impairment was more severe, with tubular cell death, tubular vacuolization, and cytoplasm shrinkage in the proximal tubule. Tubular degradation and severe necrosis were observed in some tubule parts on day 5. There were karyorrhectic tubular cells present, but there were no apparent alterations in the glomeruli. There were no kidney lesions in either the vehicle control or the CCl4-treated groups.

AKI is described as a sudden rise in serum creatinine, a reduction in urine production, or both. Besides that, AKI can be seen from the histopathological description, and in this study, which can induce the occurrence of early AKI, occurs macrophage accumulation vacuolization of tubular epithelial cells vascular dilatation hydrophilic degeneration. Similar to other research in AKI, certain studies, that use surfactant proteins A and D play a function in sepsis-induced acute kidney injury. Kidney histology in septic but not sham mice

demonstrates vacuolar degeneration of tubular cells, flattened tubular cells with tubular lumen dilatation, and a lack of brush border. The kidney injury score in septic mice is higher than in wild-type (WT) mice.[27]

This finding along with studies of the nephroprotective activity of *Zizyphus lotus* L. (ZLF) aqueous extract. The rats intoxicated with gentamicin (GM) had fewer glomeruli cells, lost tubular cell components, and experienced vascular congestion, culminating in epithelial cell atrophy. Furthermore, when compared to the healthy rats, the vulnerable foe had such a deformation of the Bowman's space as well as deformities in the epithelial membrane of the Bowman's capsule, whereas the healthy rats had a normal histoarchitecture kidney. The histoarchitecture of the kidneys is improved in animals treated with the ZLF extract and injected with GM when compared to the hazardous group. Furthermore, this histoarchitecture improvement is comparable to that of the control group.[28]

Administering water extract purple sweet potato can be used as an alternative treatment by paying attention to the appropriate dose. Further research needs to be done by increasing the dose of use that can cause mortality.

Conclusions

Overall, the results obtained in the present study have shown that the toxicity test of purple sweet potato water extracts (*Ipomoea batatas*) in the kidney exhibits minimal chemical effects, other than the expected effects as anti-inflammatory, antioxidant, and antimicrobial effects. The histopathological appearance of macrophage accumulation, vacuolization of tubular epithelial cells, vascular dilatation, and hydrophilic degeneration indicate lead to injury, but not shown mortality.

Conflict of Interest

All authors state that they have no conflicts of interest.

Acknowledgment

The authors would like to extend their sincere appreciation to the Faculty of Medicine Universitas Islam Bandung for the funding, and heartfelt gratitude to the expert team of the Department of Pathology Anatomy for a histopathological evaluation of the tissue section.

References

1. Faria J, Ahmed S, Gerritsen KGF, Mihaila SM, Masereeuw R. Kidney-based in vitro models for drug-induced toxicity testing. Arch Toxicol. 2019;93(12):3397–418.
2. Mehta RL, Awdishu L, Davenport A, Murray PT, Macedo E, Cerda J, et al. Phenotype standardization for drug-induced kidney disease. Kidney Int. 2015;88(2):226–34.
3. Izzo AA, Hoon-Kim S, Radhakrishnan R, Williamson EM. A critical approach to evaluating clinical efficacy, adverse events and drug interactions of herbal remedies. Phytother Res. 2016;30(5):691–700.
4. Uritu CM, Mihai CT, Stanciu GD, Dodi G, Alexa-Stratulat T, Luca A, et al. Medicinal plants of the family Lamiaceae in pain therapy: a review. Pain Res Manag. 2018;2018:7801543.
5. Gabriel BO, Idu M. Antioxidant property, haematinic and biosafety effect of *Ipomoea batatas* lam. leaf extract in animal model. Beni Suef Univ J Basic Appl Sci. 2021;10(1):75.
6. Musilova J, Lidikova J, Vollmannova A, Frankova H, Urminska D, Bojnanska T, et al. Influence of heat treatments on the content of bioactive substances and antioxidant properties of sweet potato (*Ipomoea batatas* L.) tubers. J Food Qual. 2020;2020:8856260.
7. Zengin G, Locatelli M, Stefanucci A, Macedonio G, Novellino E, Mirzaie S, et al. Chemical characterization, antioxidant properties, anti-inflammatory activity, and enzyme inhibition of *Ipomoea batatas* L. leaf extracts. Int J Food Prop. 2017;20(Suppl 2):1907–19.
8. Hu Y, Deng L, Chen J, Zhou S, Liu S, Fu Y, et al. An analytical pipeline to compare and characterise the anthocyanin antioxidant activities of purple sweet potato cultivars. Food Chem. 2016;194:46–54.
9. Sun H, Zhang P, Zhu Y, Lou Q, He S. Antioxidant and prebiotic activity of five peonidin-based anthocyanins extracted from purple sweet potato (*Ipomoea batatas* (L.) Lam.). Sci Rep. 2018;8(1):5018.
10. Süntar I. Importance of ethnopharmacological studies in drug discovery: role of medicinal plants. Phytochem Rev. 2020;19(5):1199–

209.
11. Wandre RA, Bhagwat GB, Solunke RS, Yadav MB, Shaikh AM. A review on medicinal plants with anti ulcer activity. J Pharmacogn Phytochem. 2013;2(1):235–40.
12. Li A, Xiao R, He S, An X, He Y, Wang C, et al. Research advances of purple sweet potato anthocyanins: extraction, identification, stability, bioactivity, application, and biotransformation. Molecules. 2019;24(21): 3816.
13. Chinedu E, Arome D, Ameh FS. A new method for determining acute toxicity in animal models. Toxicol Int. 2013;20(3):224–6.
14. Yang X, Yan X, Yang D, Zhou J, Song J, Yang D. Rapamycin attenuates mitochondrial injury and renal tubular cell apoptosis in experimental contrast-induced acute kidney injury in rats. Biosci Rep. 2018;38(6): BSR20180876.
15. Damayanti M. The ARRIVE guidelines 2.0: author checklist [Internet]. Figshare; 2022 February 14 [cited 2022 September 22]. Available from: https://figshare.com/articles/dataset/ARRIVE_Guidlines_2_0_author_checklist/19166522.
16. Tseng CY, Wang JS, Chao MW. Causation by diesel exhaust particles of endothelial dysfunctions in cytotoxicity, pro-inflammation, permeability, and apoptosis induced by ROS generation. Cardiovasc Toxicol. 2017;17(4):384–92.
17. Chen SJ, Lv LL, Liu BC, Tang RN. Crosstalk between tubular epithelial cells and glomerular endothelial cells in diabetic kidney disease. Cell Prolif. 2020;53(3):e12763.
18. Kim CS, Kim SS, Bae EH, Ma SK, Kim SW. Acute kidney injury due to povidone-iodine ingestion: a case report. Medicine (Baltimore). 2017;96(48):e8879.
19. Zhou L, Zhang C, Qiang Y, Huang M, Ren X, Li Y, et al. Anthocyanin from purple sweet potato attenuates lead-induced reproductive toxicity mediated by JNK signaling pathway in male mice. Ecotoxicol Environ Saf. 2021;224:112683.
20. Kang H, Lee SG. Protective effect of purple sweet potato leaf (*Ipomoea batatas* Linn Convolvulaceae) against alcohol-induced liver damage in mice. Trop J Pharm Res. 2021;20(2):301–8.
21. Ghasemzadeh A, Talei D, Jaafar HZE, Juraimi AS, Mohamed MTM, Puteh A, et al. Plant-growth regulators alter phytochemical constituents and pharmaceutical quality in Sweet potato (*Ipomoea batatas* L.). BMC Complement Altern Med. 2016;16:152.
22. Sutirta-Yasa IWP, Jawi IM. Antioxidant potential and hypolipidemic effects of combined purple sweet potato (*Ipomoea batatas* L.) tuber extract with honey in rats given high cholesterol feed. Bali Med J. 2017;6(3):S65–9.
23. Li CJ, Barkath AA, Abdullah MZ, Lingkan N, Ismail NHM, Pauzi SHM. The effects of citrus leaf extract on renal oxidative stress, renal function and histological changes in rats fed with heated palm oil. Biomed Pharmacol J. 2019;12(1):363–73.
24. Rahmawati IS, Soetjipto, Adi AC, Aulanni'am. Malonaldehyde level of administration ethanol extract of purple sweet potato var. Ayamurasaki in DOCA-salt hypertensive rats. J Appl Food Technol. 2018;5(1):6–9.
25. Hueper K, Gutberlet M, Rong S, Hartung D, Mengel M, Lu X, et al. Acute kidney injury: arterial spin labeling to monitor renal perfusion impairment in mice—comparison with histopathologic results and renal function. Radiology. 2014;270(1):117–24.
26. Won AJ, Kim S, Kim YG, Kim KB, Choi WS, Kacew S, et al. Discovery of urinary metabolomic biomarkers for early detection of acute kidney injury. Mol Biosyst. 2016;12(1):133–44.
27. Liu J, Abdel-Razek O, Liu Z, Hu F, Zhou Q, Cooney RN, et al. Role of surfactant proteins A and D in sepsis-induced acute kidney injury. Shock. 2015;43(1):31–8.
28. Bencheikh N, Bouhrim M, Kharchoufa L, Al Kamaly OM, Mechchate H, Es-Safi I, et al. The nephroprotective effect of *Zizyphus lotus* L. (Desf.) fruits in a gentamicin-induced acute kidney injury model in rats: a biochemical and histopathological investigation. Molecules. 2021;26(16):4806.