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RESEARCH PAPER

Dietary snakehead fish powder alleviates renal injury by suppressing oxidative stress in rat gentamicin-induced

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Abstract

Nephrotoxicity or renal injury is triggered due to the accumulation of drug levels in the kidneys causing oxidative stress. Albumin and omega-3 are known to repair and protect against tissue damage by free radicals due to oxidative stress. Snakehead fish (*Channa striata*) is a natural resource that is rich in albumin and omega-3. This study aimed to determine the nephroprotective activity of snakehead fish powder (SFP) in Wistar rats induced by gentamicin. This study used thirty male rats divided into six groups. Test animals were divided into normal control (not treated); positive control (omega-3 270 mg/kg of rat); negative control (CMC Na 0.25%); dose I (350 mg/kg SFP); dose II (700 mg/kg SFP) and dose III (1400 mg/kg SFP). All groups were induced with 100 mg/kg gentamicin intraperitoneally except for normal control. The treatment was carried out for 14 days. Rats fasted for 24 hrs after the treatment on the last day. The blood test animals were taken to measure creatinine, urea and albumin levels, then sacrificed, and their kidneys were taken for analysis of malondialdehyde (MDA) and glutathione (GSH) levels. The data obtained were statistically tested using the one-way ANOVA method and continued with post hoc LSD. The results showed the effect of SFP on the decrease in creatinine, urea, MDA, and GSH levels starting from the smallest dose of 350 mg/kg significantly compared with the negative control in gentamicin-induced Wistar rats. A higher dose of SFP can provide better nephroprotective activity. In conclusion, SFP has nephroprotective activity by suppressing oxidative stress in Wistar rats.

1. Introduction

In recent years, decreasing kidney function has shown a high potential in the critically ill and increasing the prevalence of chronic kidney disease (CKD), cardiovascular disease, and death (Chen *et al*., 2019). Drug-induced kidney injury is of grave concern among the community, which is known to be a significant contributor to kidney disease, including the incidence of acute kidney injury (AKI) and chronic kidney disease (CKD) (Joyce *et al*., 2017; Mohamed *et al*., 2019). Specific and sensitive biomarkers are rapidly required to detect and treat early-stage kidney injury. Gentamicin is a class of aminoglycoside antibiotics widely used to treat gram-negative bacterial infections. Despite its many advantages, its ability to induce acute kidney injury is the major limiting factor in the therapeutic use of gentamicin (Mohamed *et al*., 2019). Gentamicin-induced nephrotoxicity is characterized by tubular necrosis (Medić *et al*., 2019). The main target of aminoglycoside antibiotics is the proximal renal tubular cells. In this case, gentamicin will accumulate and cause nephrotoxicity via specific transporters (Morales-Alvarez, 2020). Nephrotoxicity occurs because of accumulating reactive oxygen species (ROS), which cause cell injury and necrosis via peroxidation of lipid and protein membranes and DNA damage (Sun *et al*., 2018; Sasongko *et al*., 2023). Gentamicin also induces apoptosis in the renal tubules and renal cortex and directly triggers inflammation (Randjelovic *et al*., 2017).

Oxidative stress is the major contributor to gentamicin-induced nephrotoxicity. Dietary antioxidants

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could protect the kidney against the toxicity of gentamicin. The content of albumin and omega-3 in snakehead fish has a repair and protection effect on tissue and organ damage by free radicals due to oxidative stress (Mestry *et al*., 2020; Hsueh *et al*., 2022). Snakehead fish is also a source of albumin for people with hypoalbumin (low albumin), which often occurs in patients with kidney disorders (Mulyana *et al*., 2017). Albumin in snakehead fish inhibits oxidative stress, provides anti-inflammatory effects, and works in tissue formation (Kinoshita *et al*., 2017; Yulizal *et al*., 2020). Albumin has significant antioxidant properties (Piarulli *et al*., 2022) due to the presence of a sulfhydryl group (-SH), which can function as a free radical scavenger (Pieniazek *et al*., 2018) which is implicated in the pathogenesis of inflammation (Bayarsaikhan *et al*., 2022). Omega-3 PUFAs in snakehead fish also provide antioxidative effects and provide anti-inflammatory effects (Sasongko, Zulpadly, and Farida, 2023). The use of omega-3 PUFAs is reported to have the effect of repairing damage to organs. Omega-3 PUFAs can increase catalase levels in peroxisomes and the cytoplasm resulting in improved defence against oxygen free radicals. Omega-3 PUFAs, namely EPA and DHA, can cause an increase in antioxidants and normalize excited states, control the physical status of lipids and membranes, and prevent growth in intracellular Ca in response to oxidative stress (Oppedisano *et al*., 2020). No study looks at how giving snakehead fish powder to rats with kidney damage caused by gentamicin reduces oxidative stress. This study will examine how snakehead fish powder protects against renal injury in rats with oxidative stress caused by gentamicin.

2. Materials and methods

2.1 Materials

The snakehead fish (*Channa striata*), aged 5-6 months and weighing 800-900 grams/head obtained from the cultivation site Kendal, Central Java, Indonesia.

2.2 Sample preparation

Snakehead fish are washed and cleaned of impurities such as stomach, scales, fins, tail, and head, then removed, and the meat is taken by filleting to a thickness of 0.5 cm. Fish fillet rinsed with distilled water. Snakehead fish fillets are frozen at -20ºC for a day and a night before the freeze-drying process is carried out. The sample was then dried using a vacuum freeze dryer for 72 hrs until dried snakehead fish were obtained. The dried snakehead fish is then mashed by blending it into a fine powder, and the snakehead fish powder (SFP) is stored in a desiccator until further analysis.

2.3 Animal experimental

The health research ethics committee approved the animal handling procedures and standard animal experiments of the Moewardi General Hospital with the number 1.021 / VII / HREC / 2022. For the study of the nephrotoxicity test, it was male Wistar rats aged 2-3 months weighing 170-200 g. Rats were obtained from the Animal Laboratory Pharmacology Universitas Sebelas Maret.

2.4 Study in rat renal injury models

Thirty male Wistar were divided into six groups. Group 1 was given 1 mL aquadest as a control. The negative control group was assigned CMC Na 0.25%, and the positive control group was given 270 mg/kg omega-3. The following groups received single doses of SFP at 350 mg/kg, 700 mg/kg, and 1400 mg/kg, respectively. All groups were induced by 100 mg/kg gentamicin intraperitoneally except for normal control. The test treatment was carried out for 14 days. Before being tested, the rats were conditioned for seven days. Surviving animals were weighed and observed once a day for behaviour changes, physical appearance and signs of toxicity for 14 days. The rats fasted for 24 hrs after the last day of treatment. All groups of tested animals had their blood drawn. The blood was collected and centrifuged at 3000 rpm for 10 min. The supernatant was separated to determine creatinine, urea, albumin, and total protein levels. The kidney tissue was taken to analyze malondialdehyde (MDA) and glutathione (GSH) levels.

2.5 Histological study

The kidney organs were fixed in a 10% NBF solution for histological testing. Organ tissue samples were coloured with Hematoxylin and Eosin (HE). Hematoxylin would be blue on the nucleus, and eosin would be red on the cytoplasm and extracellular matrix. Histological examination to determine the overall appearance of normal, inflammatory and necrotic kidney cells (Sasongko *et al*., 2020).

2.6 Data analysis

The data (serum creatinine, urea, albumin, total protein levels, MDA, and GSH) were statistically evaluated as mean±stadard deviation. The one-way Analysis of Variance (ANOVA) and Least Significance Different (LSD) test was performed ($p<0.05$).

3. Results

3.1 Rat body weight and organ index profile

Figure 1A shows a change in the body weight of

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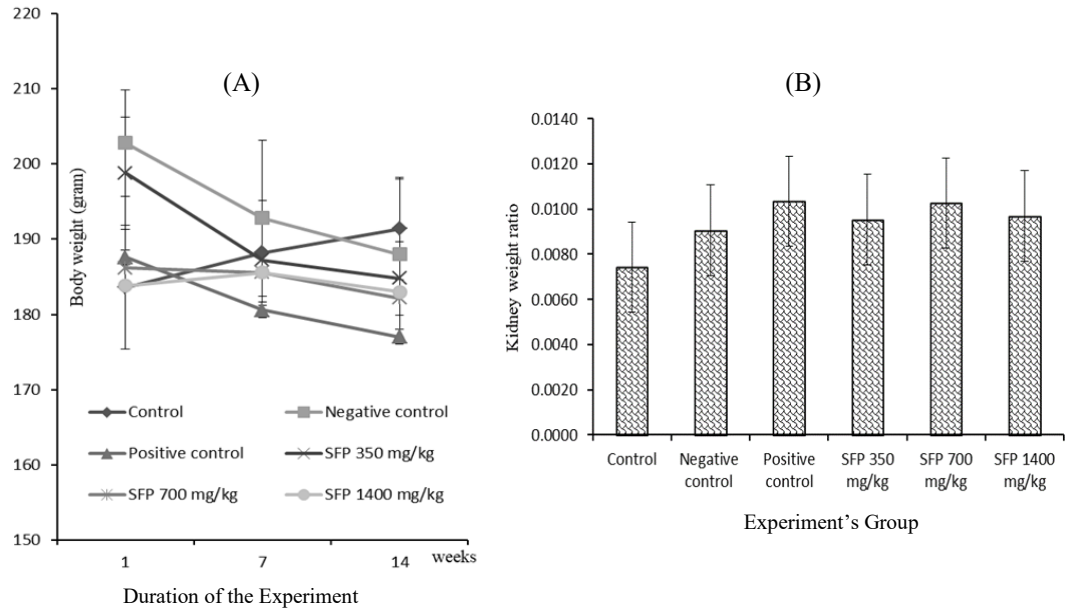

Figure 1. Body weight profile (A) and kidney weight ratio (B) of the rat after 14 days of experimental. *significantly different from the negative control ($p<0.05$).

rats, which decreased on average in all groups except the normal group. This result is due to changes in body systems due to the induction of nephrotoxicity treatment in rats. Figure 1B shows the ratio of body weight to kidney organs. The control group seems to have the smallest ratio compared to other groups. Statistically, there was no significant difference in organ ratio between the negative control group compared to other groups except the normal (control) group ($p<0.05$).

3.2 Blood biochemistry

Table 1 shows the rat's biochemical profile of kidney function after 14 days of experimental. Some signs that kidney function is worsening are high levels of creatinine, urea, albumin, and total protein in the blood. In the negative control group, there was an increase in creatinine levels (4.32 mg/dL) and urea (305.50 mg/dL). Meanwhile, creatinine levels in the control group were lower than negative controls (0.33 mg/dL). The positive control group increased creatinine levels by 0.83 mg/dL. This condition shows that the activity of omega-3 can inhibit the occurrence of kidney damage by inducing gentamicin. The mean increase in creatinine levels for treatment with 350 mg/kg SFP was 1.98 mg/dL; treatment with SFP at the dose of 700 mg/kg was 1.13 mg/dL, and treatment with 1400 mg/kg SFP was 1.037 mg/dL. Compared with the positive control, treatment with SFP at doses of 700 mg/kg and 1400 mg/kg did not have a significant difference ($p>0.05$). This shows that snakehead fish powder may be able to lower creatinine levels, just like the positive control, even though gentamicin-induced rats still have higher creatinine levels than normal. Treatment with 350 mg/kg SFP differs significantly from the negative and positive controls ($p<0.05$), indicating that snakehead fish powder at 350 mg/kg has lower nephroprotective activity than the positive control. Table 1 shows that biochemical blood levels are similar to the creatinine profile. The average increase in urea levels in the negative group was significantly different from the other groups ($p<0.05$). However, there was no significant difference in each group's albumin and total protein content. Administration of SFP starting at a dose of 350 mg/kg significantly reduced blood creatinine levels in rats ($p<0.05$). They can lower blood creatinine and urea levels at 700 mg/kg and 1400 mg/kg ($p<0.05$).

Table 1. The blood biochemical profile of kidney function of the rat after 14 days of experimental.

Group	Blood biochemical profile of kidney function			
	Creatinine (mg/dL)	Urea (mg/dL)	Albumin (g/L)	Total Protein (g/L)
Control	0.33±0.03*	36.20±3.77*	33.73±1.28	78.07±3.23
Negative control	4.32±1.09	305.50±37.02	32.56±0.72	75.28±2.16
Positive control	0.83±0.05*	153.17±21.58*	31.36±0.47	79.39±2.42
SFP 350 mg/kg	1.98±0.26*	337.60±34.07	30.82±1.21	77.58±6.79
SFP 700 mg/kg	1.13±0.16*	188.83±18.21*	32.23±0.23	73.33±3.28
SFP 1400 mg/kg	1.04±0.22*	103.93±15.68*	33.98±1.01	77.51±1.92

*significantly different from the negative control ($p<0.05$).

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3.2 Malondialdehyde and glutathione profile

Figures 2 and 3 show the profile of the levels of MDA and GSH in the kidney organs of rats after 14 days of experimentation. Malondialdehyde levels in the negative control group had the highest value. This condition shows that gentamicin injection can increase MDA levels in rat kidney organs. Malondialdehyde is a metabolite of lipid peroxidation by free radicals. Malondialdehyde can be formed when hydroxyl free radicals such as reactive oxygen species (ROS) react with fatty acid components of cell membranes, resulting in a chain reaction known as lipid peroxidation (Sasongko *et al*., 2018). The lipid peroxidation reaction will break the chain of fatty acids into different toxic compounds that will damage the cell membranes. Figure 2 shows that the administration of SFP at a dose of 350 mg/kg, 700 mg/kg and 1400 mg/kg significantly reduced MDA levels during the 14 days of the experiment ($p<0.05$). Meanwhile, Figure 3 shows the lowest GSH levels in the negative control group. Glutathione is a primary antioxidant that prevents the formation of new free radicals by converting existing free radicals into molecules with fewer active effects (Gaucher *et al*., 2018). When 100 mg/kg of gentamicin was given, the levels of antioxidants made by the body were significantly lowered. This result was evident when the GSH levels in the normal control group were compared to those in the negative control group. After the administration of SFP doses of 700 mg/kg and 1400 mg/kg, there was a significant increase in GSH levels ($p<0.05$).

3.3 Histopathological evaluation

Figure 4 shows the histopathological evaluation of kidney tissue. In the normal group, the tubules and glomerulus still look normal. In the negative control group, most tubules appeared necrotic (N). In the group of rats given SFP with dosage levels of 300 mg/kg, 700 mg/kg, and 1400 mg/kg, the amount of necrosis was less than in the negative control group.

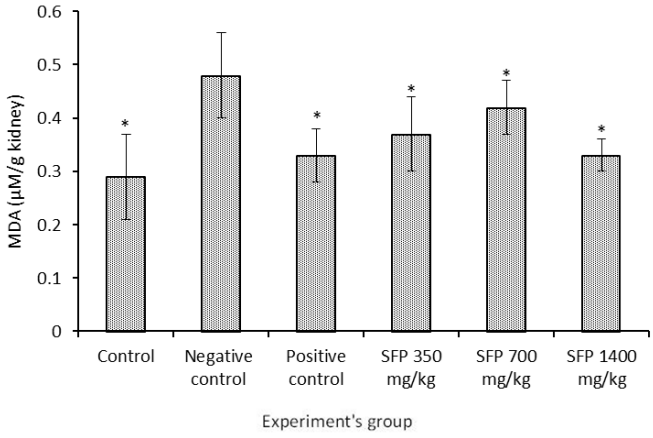

Figure 2. Malondialdehyde level of the rat after 14 days of experimental. *significantly different from the negative control ($p<0.05$).

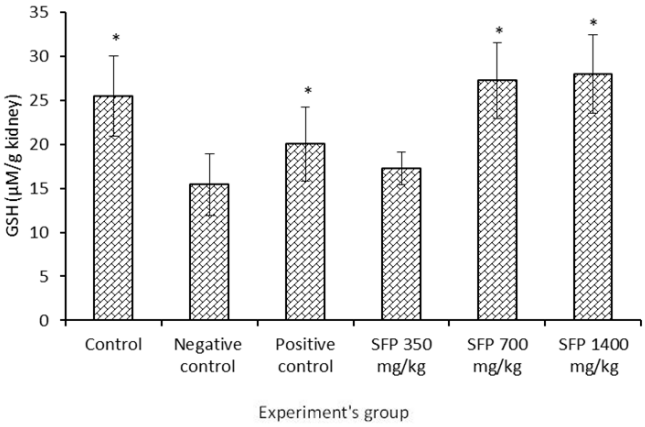

Figure 3. Glutathione level of the rat after 14 days of experimental. *significantly different from the negative control ($p<0.05$).

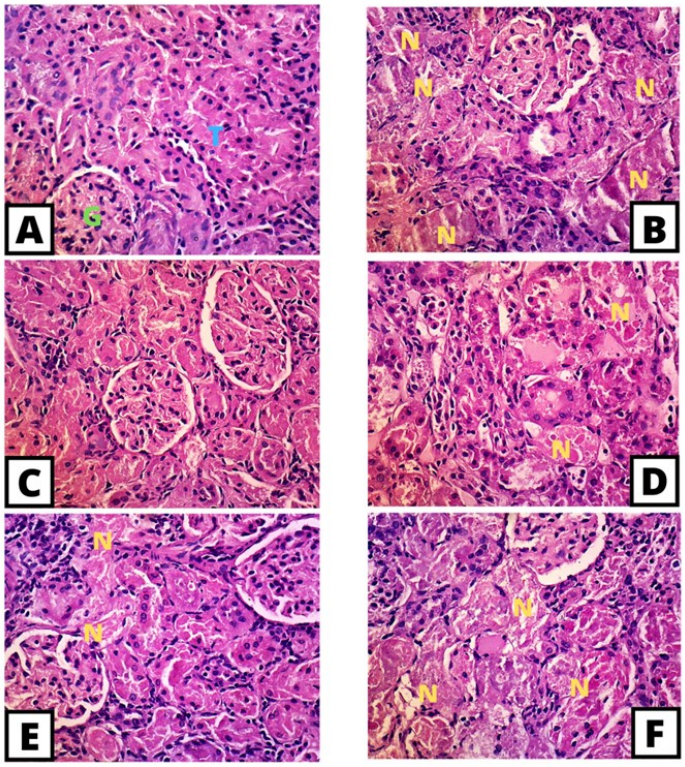

Figure 4. Effects administration SFP on the histology of renal tissue with 400× magnification. (A) Control, (B) Positive control, (C) Negative control, (D) nephrotoxicity with SFP 350 mg/kg administration, (E) nephrotoxicity with SFP 700 mg/kg administration, (F) nephrotoxicity with SFP 1400 mg/kg administration. G (glomerulus) and T (tubules), N (tubules appeared necrotic).

4. Discussion

This study aimed to determine the influence of the administration of snakehead fish powder on alleviating renal injury through observations of blood biochemical, oxidative stress, and histological in rat models. Figure 1 shows that the animals in the gentamicin-induced group lost weight more quickly than those in the normal group. This condition was because gentamicin stopped the

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animals from taking in food and water and making proteins (Adil *et al*., 2016). Acute renal dysfunction in gentamicin-induced rats was evidenced by a significant increase in serum creatinine and weight loss (Ogundipe *et al*., 2017). Creatinine and urea levels can be used to measure impaired kidney function. An increase in creatinine and urea levels in the blood indicates a decrease in the kidneys' filtration process (Zhang *et al*., 2018). They are a waste product of the body's metabolism that is constantly made, filtered by the kidneys, not reabsorbed, and secreted by the proximal tubule. This makes it a suitable marker for measuring kidney function. Normal creatinine values in rats ranged from 0.5-1.0 mg/dL (Butt *et al*., 2019), and the standard value of plasma urea concentration is 20 - 40 mg/dL (Vysakh *et al*., 2018). The test results showed that the administration of SFP at 700 mg/kg and 1400 mg/kg inhibited increased serum creatinine and urea levels. Albumin and protein levels are a marker test of the incidence of albumin loss through the kidneys but cannot be a specific parameter that indicates kidney damage. Tests for albumin and protein levels were used as a follow-up test after testing for creatinine levels. Hypoalbumin and hypoprotein are caused by less albumin-protein being made or more albumin-protein leaving the body through the kidneys (Gounden *et al*., 2022).

Malondialdehyde levels in the body can describe the condition of body organs due to lipid peroxidation by free radicals. MDA levels are also markers of cellular damage caused by free radicals (Sutaria *et al*., 2022). Gentamicin can cause nephrotoxicity, which is damage to the kidneys. This damage is caused by the buildup of ROS and free radicals, which damage membrane lipids and proteins and damage DNA (Quiros *et al*., 2011). The increase in MDA levels indicates increasing free radicals and decreasing antioxidants in the body (Akure *et al*., 2020). A significant decrease in GSH levels in kidney injury could be caused by an increase in ROS in the form of nitric oxide radicals, which react with superoxide radicals to form H_2O_2 compounds. The increase in free radicals can reduce endogenous antioxidants such as GSH, which causes oxidative stress and results in damage to kidney cells (Qi and Dong, 2021). The increase in GSH levels shows that the omega-3 content in SFP can help the endogenous antioxidants present in the body to counteract free radicals caused by reactive metabolites of gentamicin. This study is supported by the statistical results, where the positive group was not significantly different from the group given SFP. Omega -3 has antioxidative effects and anti-inflammatory effects, which can lead to increased antioxidants, normalizing excited states, and control the physical status of lipids and membranes (Li and Song, 2022). Omega-3 prevents lipid peroxidation and protects against oxidative stress by lowering levels of MDA and increasing levels of GSH (Pineda-Peña *et al*., 2018).

5. Conclusion

Induction of renal injury in rats caused by gentamicin induction can be attenuated by the administration of SFP starting at a dose of 350 mg/kg. Oxidative stress inhibition prevents kidney damage, characterized by a decrease in MDA levels and an increase in GSH levels after giving SFP for 14 days. A higher dose of SFP can provide better nephroprotective activity. In future research, measuring inflammatory markers and protein expression will be very important to figure out how SFP protects the kidneys.

Conflict of interest

The authors declare no conflict of interest.

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References

Adil, M., Kandhare, A.D., Dalvi, G., Ghosh, P., Venkata, S., Raygude, K.S. and Bodhankar, S.L. (2016). Ameliorative effect of berberine against gentamicin-induced nephrotoxicity in rats via attenuation of oxidative stress, inflammation, apoptosis and mitochondrial dysfunction. *Renal Failure*, 38(6), 996 –1006. https:// doi.org/10.3109/0886022X.2016.1165120

Akure, Y.J., Ahmed, M., Bukar, H. and Simon, G. (2020). Short term effect of zinc administration on some biochemical parameters and antioxidant enzymes in albino rats. *International Journal of Life Sciences and Biotechnology,* 3(3), 317–324. https:// doi.org/10.38001/ijlsb.741158

Bayarsaikhan, G., Bayarsaikhan, D., Lee, J. and Lee, B. (2022). Targeting Scavenger Receptors in Inflammatory Disorders and Oxidative Stress. *Antioxidants*, 11(5), 936. https://doi.org/10.3390/

antiox11050936

Butt, M.S., Randhawa, M.A. and Shahid, M. (2019). Nephroprotective effects of red beetroot-based beverages against gentamicin-induced renal stress. *Journal of Food Biochemistry*, 43(7), 12873. https://doi.org/10.1111/jfbc.12873

Chen, T.K., Knicely, D.H. and Grams, M.E. (2019). Chronic Kidney Disease Diagnosis and Management: A Review. *Journal of the American Medical Association,* 322(13), 1294–1304. https://doi.org/10.1001/jama.2019.14745

Gaucher, C., Boudier, A., Bonetti, J., Clarot, I., Leroy, P. and Parent, M. (2018). Glutathione: Antioxidant Properties Dedicated to Nanotechnologies. *Antioxidants*, 7(5), 62. https://doi.org/10.3390/antiox7050062

Gounden, V., Bhatt, H. and Jialal, I. (2022). Renal Function Tests. In StatPearls. Treasure Island, Florida, USA: StatPearls Publishing.

Hsueh, Y.J., Chen, Y.N., Tsao, Y.T., Cheng, C.M., Wu, W.C. and Chen, H.C. (2022). The Pathomechanism, Antioxidant Biomarkers, and Treatment of Oxidative Stress-Related Eye Diseases. *International Journal of Molecular Sciences*, 23(3), 1255. https://doi.org/10.3390/ijms23031255

Joyce, E.L., Kane-Gill, S.L., Fuhrman, D.Y. and Kellum, J.A. (2017). Drug-Associated Acute Kidney Injury: Who's at risk?. *Pediatric Nephrology*, 32(1), 59–69. https://doi.org/10.1007/s00467-016-3446-x

Kinoshita, H., Watanabe, K., Azma, T., Feng, G.G., Akahori, T., Hayashi, H., Sato, M., Fujiwara, Y. and Wakatsuki, A. (2017). Human serum albumin and oxidative stress in preeclamptic women and the mechanism of albumin for stress reduction. *Heliyon*, 3(8), 00369. https://doi.org/10.1016/j.heliyon.2017.e00369

Li, P. and Song, C. (2022). Potential treatment of Parkinson's disease with omega-3 polyunsaturated fatty acids. *Nutritional Neuroscience*, 25(1), 180–191. https://doi.org/10.1080/1028415X.2020.1735143

Medić, B., Stojanović, M., Rovčanin, B., Kekić, D., Škodrić, S.R., Jovanović, G.B., Vujović, K.S., Divac, N., Stojanović, R., Radenković, M. and Prostran, M. (2019). Pioglitazone attenuates kidney injury in an experimental model of gentamicin-induced nephrotoxicity in rats. *Scientific Reports* 9, 13689. https://doi.org/10.1038/s41598-019-49835-1

Mestry, S.N., Gawali, N.B., Pai, S.A., Gursahani, M.S., Dhodi, J.B., Munshi, R. and Juvekar, A.R. (2020). Punica granatum improves renal function in gentamicin-induced nephropathy in rats via attenuation of oxidative stress. *Journal of Ayurveda and Integrative Medicine*, 11(1), 16–23. https://doi.org/10.1016/j.jaim.2017.09.006

Mohamed, D.I., Khairy, E., Saad, S.S.T., Habib, E.K. and Hamouda, M.A. (2019). Potential protective effects of Dapagliflozin in gentamicin induced nephrotoxicity rat model via modulation of apoptosis associated miRNAs. *Gene*, 707, 198–204. https://doi.org/10.1016/j.gene.2019.05.009

Morales-Alvarez, M.C. (2020). Nephrotoxicity of Antimicrobials and Antibiotics. *Advances in Chronic Kidney Disease, Toxicology for Nephrologists*, 27 (1), 31–37. https://doi.org/10.1053/j.ackd.2019.08.001

Mulyana, R., Setiati, S., Martini, R.D., Harimurti, K. and Dwimartutie, N. (2017). The Effect of *Ophiocephalus striatus* Extract on the Levels of IGF-1 and Albumin in Elderly Patients with Hypoalbuminemia. *Acta Medica Indonesiana*, 49(4), 324–329.

Ogundipe, D.J., Akomolafe, R.O., Sanusi, A.A., Imafidon, C.E., Olukiran, O.S. and Oladele, A.A. (2017). *Ocimum gratissimum* Ameliorates Gentamicin-Induced Kidney Injury but Decreases Creatinine Clearance Following Sub-Chronic Administration in Rats. *Journal of Evidence-Based Complementary and Alternative Medicine*, 22(4), 592–602. https://doi.org/10.1177/2156587217691891

Oppedisano, F., Macrì, R., Gliozzi, M., Musolino, V., Carresi, C., Maiuolo, J., Bosco, F., Nucera, S., Caterina Zito, M., Guarnieri, L., Scarano, F., Nicita, C., Coppoletta, A.R., Ruga, S., Scicchitano, M., Mollace, R., Palma, E. and Mollace, V. (2020). The Anti-Inflammatory and Antioxidant Properties of n-3 PUFAs: Their Role in Cardiovascular Protection. *Biomedicines*, 8(9), 306. https://doi.org/10.3390/biomedicines8090306

Piarulli, F., Banfi, C., Brioschi, M., Altomare, A., Ragazzi, E., Cosma, C., Sartore, G. and Lapolla, A. (2022). The Burden of Impaired Serum Albumin Antioxidant Properties and Glyco-Oxidation in Coronary Heart Disease Patients with and without Type 2 Diabetes Mellitus. *Antioxidants*, 11(8), 1501. https://doi.org/10.3390/antiox11081501

Pieniazek, A., Gwozdzinski, L., Zbrog, Z. and Gwozdzinski, K. (2018). Alterations in conformational state of albumin in plasma in chronic hemodialyzed patients. *PLoS One*, 13(3), e0192268. https://doi.org/10.1371/journal.pone.0192268

Pineda-Peña, E.A., Martínez-Pérez, Y., Galicia-Moreno, M., Navarrete, A., Segovia, J., Muriel, P., Favari, L., Castañeda-Hernández, G. and Chávez-Piña, A.E.

(2018). Participation of the anti-inflammatory and antioxidative activity of docosahexaenoic acid on indomethacin-induced gastric injury model. *European Journal of Pharmacology*, 818, 585–592. https://doi.org/10.1016/j.ejphar.2017.11.015

Qi, J. and Dong, F. (2021). The relevant targets of antioxidative stress: a review. *Journal of Drug Targeting*, 29(7), 677–686. https://doi.org/10.1080/1061186X.2020.1870987

Quiros, Y., Vicente-Vicente, L., Morales, A.I., López-Novoa, J.M. and López-Hernández, F.J. (2011). An Integrative Overview on the Mechanisms Underlying the Renal Tubular Cytotoxicity of Gentamicin. *Toxicological Sciences*, 119(2), 245–256. https://doi.org/10.1093/toxsci/kfq267

Randjelovic, P., Veljkovic, S., Stojiljkovic, N., Sokolovic, D. and Ilic, I. (2017). Gentamicin nephrotoxicity in animals: Current knowledge and future perspectives. *EXCLI Journal*, 16, 388–399. https://doi.org/10.17179/excli2017-165

Sasongko, H., Efendi, N.R. and Sugiyarto (2018). The ethanolic extract of mountain papaya (*Vasconcellea pubescens* A.DC.) fruit against lipid peroxidation of rat liver tissues. *AIP Conference Proceedings*, 2019, 050001. https://doi.org/10.1063/1.5061894

Sasongko, H., Lestari, R., Yugatama, A. and Farida, Y. (2020). Antidiabetic and Antioxidant Effect Combination *Vasconcellea pubescens* A.DC. and *Momordica charantia* L. Extract in Alloxan- Induced Diabetic Rats. *Pharmacognosy Journal*, 12(2), 311–315. https://doi.org/10.5530/pj.2020.12.49

Sasongko, H., Nurrochmad, A., Nugroho, A.E. and Rohman, A. (2023). Fish oil supplementation in diabetic nephropathy prevents: inflammatory and oxidative stress target. *Food Research*, 7(2), 307-315. https://doi.org/10.26656/fr.2017.7(2).220

Sasongko, H., Zulpadly, M.H. and Farida, Y. (2023). An evaluation of potential fatty acids nutrition in snakehead fish (*Channa striata*) waste. *Food Research*, 7(4), 30-35. https://doi.org/10.26656/fr.2017.7(4).285

Sun, M.-S., Jin, H., Sun, X., Huang, S., Zhang, F.L., Guo, Z.N. and Yang, Y. (2018). Free Radical Damage in Ischemia-Reperfusion Injury: An Obstacle in Acute Ischemic Stroke after Revascularization Therapy. *Oxidative medicine and cellular longevity*, 2018, 3804979. https://doi.org/10.1155/2018/3804979

Sutaria, S.R., Gori, S.S., Morris, J.D., Xie, Z., Fu, X.A. and Nantz, M.H. (2022). Lipid Peroxidation Produces a Diverse Mixture of Saturated and Unsaturated Aldehydes in Exhaled Breath That Can Serve as Biomarkers of Lung Cancer—A Review. *Metabolites*, 12(6), 561. https://doi.org/10.3390/metabo12060561

Vysakh, A., Abhilash, S., Kuriakose, J., Midhun, S.J., Jyothis, M. and Latha, M. (2018). Protective effect of *Rotula aquatica* Lour against gentamicin induced oxidative stress and nephrotoxicity in Wistar rats. *Biomedicine and Pharmacotherapy*, 106, 1188–1194. https://doi.org/10.1016/j.biopha.2018.07.066

Yulizal, O.K., Lelo, A., Ilyas, S. and Kusumawati, R.L. (2020). The effect of Channa striata extract and standard eradication regimen on asymmetric dimethylarginine in *Helicobacter pylori* gastritis rat model. *Veterinary World*, 13(8), 1605–1612. https://doi.org/10.14202/vetworld.2020.1605-1612

Zhang, J., Liu, J. and Qin, X. (2018). Advances in early biomarkers of diabetic nephropathy. *Revista da Associacao Medica Brasileira*, 64(1), 85–92. https://doi.org/10.1590/1806-9282.64.01.85

