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# Treatment with celery (Apium graveolens L) extract alleviated pancreas and liver cell-injury with improved serum parameters in diabetic rats

**Andrew Johan[1], Jodelin Muninggar[1]**

[1]Medical Study Program, Faculty of Medicine and Health Sciences, Universitas Kristen Satya Wacana. Jl. Diponegoro No.52-60, Salatiga, Sidorejo, Kota Salatiga, Jawa Tengah 50711, Indonesia

Orcid ID
Andrew Johan 0000-0002-9854-7607
Jodelin Muninggar 0000-0003-3028-4182
**corresponding author**: andrewjohan@fk.undip.ac.id

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**Abstract**

Celery had been reported as phytochemical antioxidants that contained abundance of flavonoids. Previous studies in diabetic rats and humans reported that reactive oxygen species (ROS) caused further damage to organs, like pancreas, liver. The present study was proposed to discover the benefits of celery on pancreas and liver cell-injury, serum glucose, lipids, and liver enzymes in diabetic rats. Methods: Eighteen diabetic rats with serum glucose more than 200mg/dL were randomly divided into three groups. Group 1, diabetic rats were not given any antioxidants; Groups 2 and 3 diabetic rats were treated with celery orally at 200 mg/kg BW/day and 400 mg/kg BW/day, respectively. After six weeks, the overnight fasting blood was gained from the retro-orbital plexus and centrifuged at 4000 rpm to obtain serum. The animals were sacrificed to harvest the pancreas and liver. The organs were processed in formalin-fixed and paraffin-embedded tissues. Results: Severe pancreas and liver cell-damage appeared in Group 1, while moderate and mild damage in Groups 2 and 3. Serum parameters were improved in Groups 2 and 3 compared to Group1. Conclusions: Treatment with celery extract reduced pancreas and liver injury and repaired the serum parameters in diabetic rats.

**Key words**: celery, diabetic rats, liver, pancreas, serum parameters

## Introduction

Diabetes is a chronic and metabolic disease characterized by high blood glucose levels. WHO (2021 announced that diabetes has become a pressing global health concern. Its prevalence is rising dramatically over the past three decades, affecting countries of all income levels. The prevalence of diabetes and obesity has been steadily increasing in this world. estimated that the number of diabetic patient will go up to 700 million by 2045. Previous studies in diabetic rats and humans reported that reactive oxygen species (ROS) caused further damage to organs, like pancreas, liver, and kidney. Elevated of indicators of tissue oxidative stress have been noticed. The 8-hydroxy-2'-deoxyguanosine (8-OHdG) was identified along with 4-hydroxy-2-nonenal (HNE)-that modified proteins and caused fibrosis of the pancreatic organ.[3]

Increased lipid peroxidation, liver enzymes, and reduced liver weight were found in diabetic rats.[4] Oxidative stress caused insulin resistance,[5] it happened before the development of fatty liver in humans.[6] ROS provoked endoplasmic reticulum oxidative stress with renal tubular apoptosis in diabetic mice.[7]

Antioxidants extracted from plants had been The International Diabetes Federation (IDF) helpful to decrease complications in diabetic animals. Decreased apoptotic cells and lipid peroxidation in kidney tissue were observed in diabetic rats administered with extract of Pueraria tuberosa.[8] Flower and stalk of plant Musa balbisiana decreased the serum levels of malondialdehyde (MDA), triglyceride, low density lipoprotein (LDL), and total cholesterol.[9] Other antioxidants, such as quercetin,[10] resveratrol,[11] Alcea rosea seeds[12] and theaflavin.[13] also proved to have beneficial effects in diabetic animals.

Celery (Apium graveolens L) is an edible plant from the apiaceae family, it grows in all districts of Europe, Africa and Asia.[14] Celery had been reported as phytochemical antioxidants that consist of caffeic acid, p-coumaric acid, ferulic acid, apigenin, luteolin, tannin, saponin, and kaempferol.[15] Celery extracts reduced xanthine oxidase (XO) and lipid peroxidation from liver tissue homogenate and decreased serum uric acid level in hyperuricemic mice.[16,17] It decreased the activity of monoamine oxidase and protected dopaminergic neurons Parkinson's disease (PD) model mice,[18] declined serum creatinine, urea , and area of the renal tissue lesion in 3-chloro-1, 2-propanediol (3-MCPD)-induced renal injury,[19] and decreased retinal oxidative damage.[20] The hypothesis of this study was : celery extracts could lowered the histopathologic tissue damage of pancreas and liver organs in diabetic rats and could decrease the levels of serum glucose, triglyceride, total cholesterol, alanine transaminase, and aspartate transferase.

## Ethical Clearance

This research had been approved by the Health Research Ethics Commission of the Faculty of Medicine, Diponegoro University, Semarang with No. 88 / EC / H / FK-UNDIP/IX/ 2020.

## Materials and Methods

### Celery extract

The fresh leaves with stalks of celery of were harvested from traditional herb garden in Tawangmangu, Jawa Tengah, Indonesia. It has a subtropical climate and located at medium-high altitude land with 1.800 meters above sea water. The whole plant was washed, dried in incubator at $60^0$ C for 1 hour, and grounded to a fine powder with a blender. The celery powder was kept in refrigerator with temperature $4^0$ C before use. Celery extract was made fresh every day by adding to boiling water and let it cool in room temperature.

### Diphenyl-2-picrylhydrazyl DPPH test

The capacity to neutalise reactive oxygen species of celery extract was measured with previously reported procedure.[21] The celery extract was poured in 160 µM DPPH radical in a methanol solution. Then it was incubated at room temperature in the dark for 20 minutes. The end product was a yellow-colored diphenylpicrylhydrazine, it was read in visual light spectrophotometer at 517 nm. The inhibitory percentage of DPPH was calculated according to the standard known formula. Scavenging activity (%) = [(absorbance of the control - absorbance of the sample)/absorbance of the control] × 100%. In the present study, the scavenging activity of the celery extract was 69.4%.

### Animal treatment

Adults male Sprague-Dawley rats at 200 – 230 gram body weight were obtained from public University of Semarang, Central Java, Indonesia. The rats were kept at 25 ± 5 °C in a well-ventilated animal plastic chambers under a 12:12 h light/dark cycle, with free access to food and water. The rats were induced with single dose alloxan 70 mg/kg BW intra-peritoneal (ip) and given orally 20% sugar solution in tap wateras the only beverage during the study. Three days after induced by alloxan and sugar in take, hyperglycemic rats with blood sugar more than 200 mg/dL were randomly divided into 3 groups (n=6).

Group 1, diabetic rats were not given any antioxidants nor medication; Groups 2, diabetic rats were administered with celery at 200 mg/kgBW/day per-os. Group 3, diabetic rats treated with 400 mg/kgBW/day per-os. After 6 weeks, the overnight fasting blood was gained from retro-orbital plexus and centrifuged at 4000 rpm to obtain serum. The animals were sacrificed to harvest pancreas and liver intack organs. The organs will be processed to observe histopathologic findings in formalin-fixed and paraffin-embedded (FFPE) tissues stained with hematoxylin and eosin (HE).

The serum levels of glucose was determined by spectrophotometer using enzyme glucose oxidase (GOD) to generate hydrogen-peroxide ($H_2O_2$) that would oxidize the substrate N,N-diethyl-p-phenylenediamine to form a purple color.[22] Triglyceride determination using GPO-PAP (DiaSys) was done by adding 2, 4-chlorophenol, ATP, Mg2+, glycerocination, peroxidase, lipoprotein lipase, 4-aminiantipirin, and glycerol 3-phosphate-oxidase. The product was measured at 500 nm. Total Cholesterol was determined by colorimetry enzymatic cholesterol p-aminophenazone cholesterol method (CHOD-PAP,DiaSys).[23] Serum AST and ALT determination were based on colored formazan produced by the reduction of the tetrazolium salt INT with NADH, electron transfer being facilitated by PMS; the formazan was stable and the extinction was read at 500 nm.[24]

## Results

### Bennefit Effects of Celery Extract on Histopathologic findings of pancreas beta cells in diabetic rats.

The microscopic findings in the present study were decreased □eta pancreas cells in islet Langerhans (Fig.1). The number of normal cells were severely decreased in diabetic rats without antioxidant treatment. Celery extract increased the number of normal pancreatic cells in diabetic rats. High dose (400 mg/kg BW/day) showed better appearance of beta cells in diabetic rats.

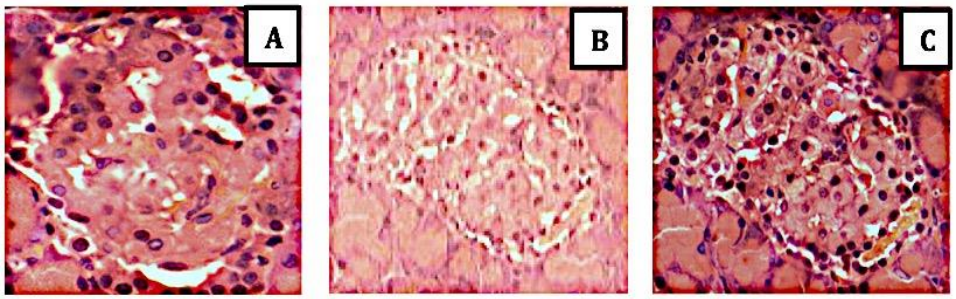


Fig 1. Decreased beta cells in Islet Langerhans
A. Severe decreased beta cells in diabetic rats
B. Moderate decreased beta cells in diabetic rats treated with low dose celery
C. Mild decreased beta cells in diabetic rats treated with high dose celery

**Bennefit Effects of Celery Extract on Histopathologic findings of liver tissue damage in diabetic rats.**

The histopathological damage in liver tissue shown as macrovesicular steatosis. The microscopic findings showed severe steatosis in the liver tissue of diabetic rats without any medication. Treatment with celery extract ameliorated the degree of liver steatosis (figure 2). High dose (400 mg/kg BW/day) showed better appearance of liver tissue.

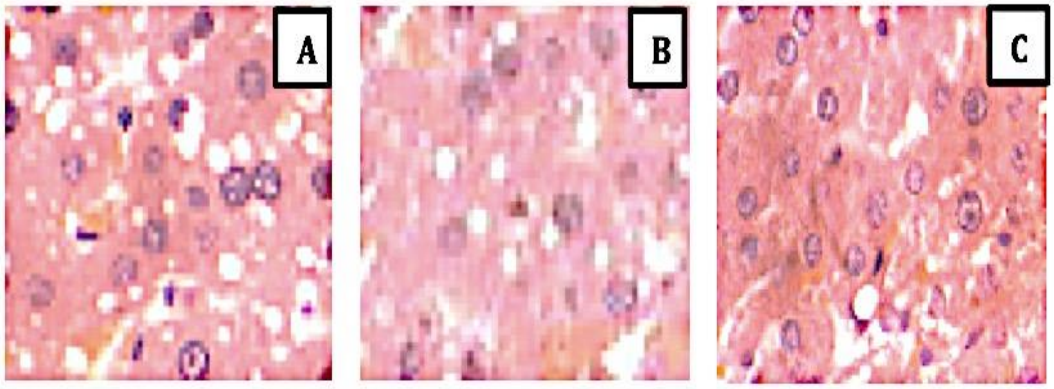


Fig 2. Macrovesicular steatosis in liver tissue
A. Severe macrovesicular steatosis in diabetic rats
B. Moderate macrovesicular steatosis in diabetic rats treated with low dose celery
C. Mild macrovesicular steatosis in diabetic rats treated with high dose celery

**Bennefit Effects of Celery extract on The levels of serum glucose in diabetic rats**

The levels of serum glucose were significantly higher in diabetic rats without any medication. The group of rats treated with celery exract significantly had lower serum glucose (figure 3). Both low dose (200 mg/kg BW/day) and high dose (400 mg/kg BW/day) of celery extract that were administered to diabetic rats significantly decreased the level of serum glucose with $p < 0.05$. Treatment celery with higher dose (400 mg/KgBW/day) did not cause hypoglicemic case. It did not lowered the levels of serum glucose compared to the smaller dose (200 mg/KgBW/day)

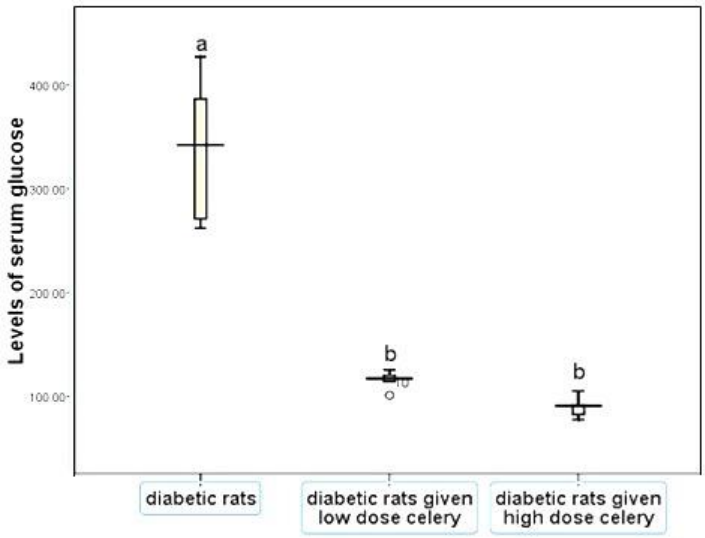


Fig 3. Effects of celery on levels of serum glucose in diabetic rats

**Bennefit Effects of Celery Extract on The levels of serum trigliseride in diabetic rats**

The levels of serum trigliseride were significantly higher in diabetic rats without any medication. The group of rats treated with celery exract significantly had lower serum trigliseride (figure 4). Both low dose and high dose of celery extract that were administered to diabetic rats significantly decreased the level of serum trigliseride with $p < 0.05$.

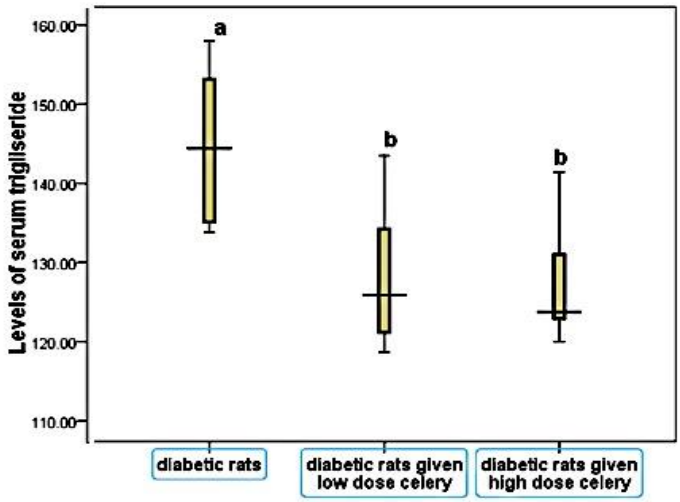


Fig 4. Effects of celery on levels of serum triglyceride in diabetic rats

**Bennefit Effects of Celery extract on The levels of serum total cholesterol in diabetic rats**

The levels of serum total cholesterol were significantly higher in diabetic rats without any medication. The group of rats treated with celery exract significantly had lower serum total cholesterol (figure 5). High dose of celery extract (400 mg/kg BW/day) that was administered to diabetic rats significantly decreased the levels of serum total cholesterol with $p < 0.05$. However, low dose (200 mg/kg BW/day) of celery did not alter the level of total cholesterol in diabetic rats.

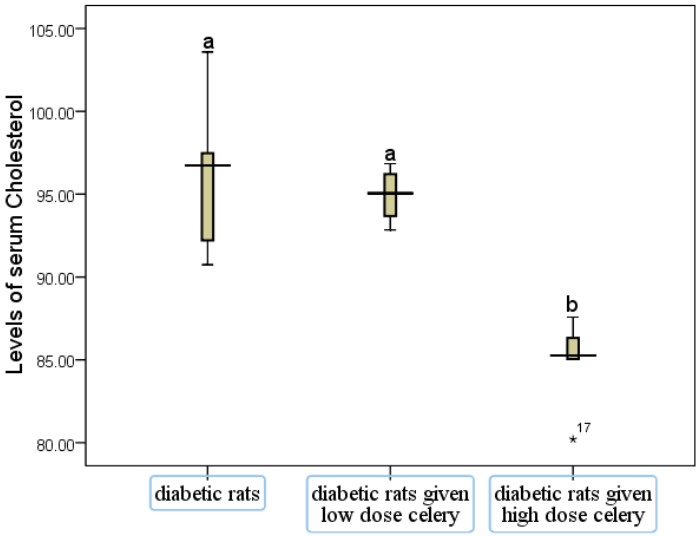


Fig 5. Effects of celery on levels of serum total cholesterol in diabetic rats

**Bennefit Effects of Celery extract on Levels of serum aspartate aminotransferase and alanine transferase**

Levels of serum alanine transferase significantly decreased in rats administered with celery, but the levels of aspartate aminotransferase did not show differences among the groups.(table 1).

Table 1. Levels of serum AST and ALT in diabetic rats

| Serum | Diabetic rats | Diabetic rats with low dose celery | Diabetic rats with high dose celery |
|---|---|---|---|
| AST (U/L) | 40.78 ± 4.18 | 35.25 ± 6.27 | 39.21 ± 7.8 |
| ALT (U/L) | 31.79 ± 8.17 | *17.73 ± 3.43 | *24.25 ± 8.8 |

AST: aspartate aminotransferase
ALT: alanine transaminase

**Discussion**

Celery had been reported to have antioxidant effects, while diabetic rats suffered complication due to oxidative stress. Therefore, it was hypothetically assumed that celery extract could ameliorate the tissue damage of pancreas and liver in diabetic rats

The conceptual frame of this study was constructed below (Fig.6)

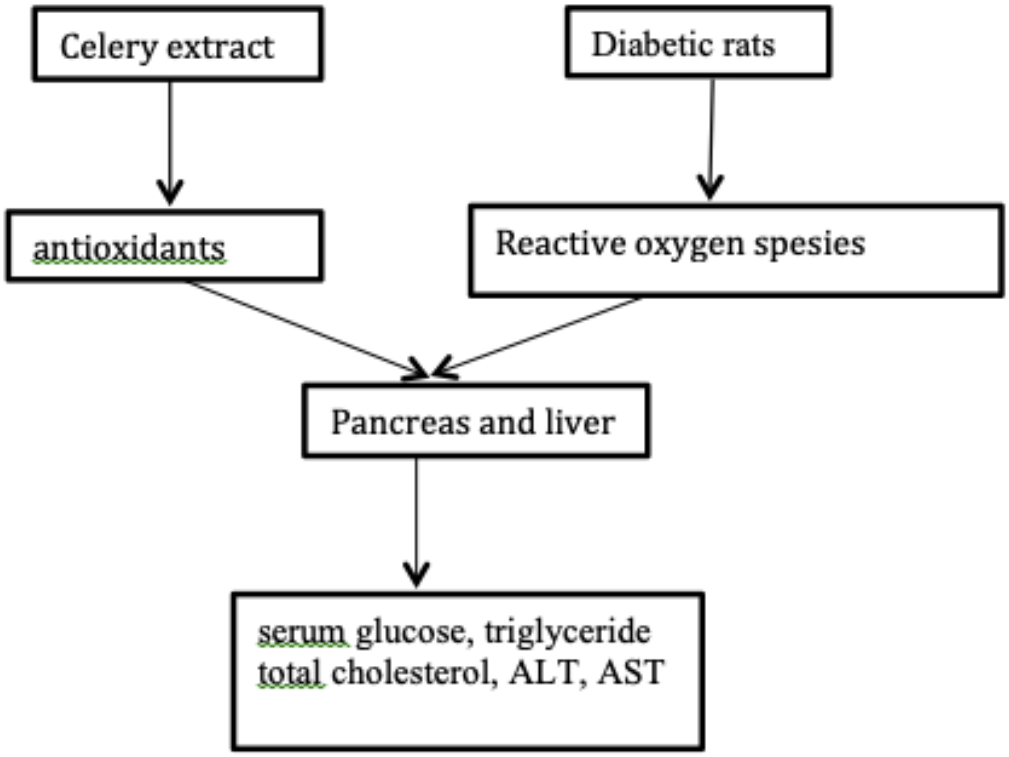


Fig 6. The conceptual framework of this study

Previous studies encouraged researchers to gain the benefits of celery for treatment and prevention of metabolic diseases.[25] Serious side effects were not reported in humans who routinely consumed the raw herb.[26,27] It was analyzed to bear phytochemical medicine such as alkaloids, steroids, flavonoids, vitamins A and C.[28,29] The leaf extract was revealed to have flavonoids, phenols, tannin, and saponins.[30] The flavonoid compounds could block the activity of digestive enzymes on carbohydrate in particular α-glucosidase and α-amylase.[31] Diabetic rats and humans had been declared that they suffered oxidative stress. The peripheral blood mononuclear cells (PBMC) produced higher oxygen radicals.[32] Human serum albumin (HSA) mixed with glucose in vitro yielded glycated protein that produced superoxide radical.[33] Mitochondrial superoxide radical was higher in diabetic patient,[34] increased plasma lipid peroxide was found in pregnant women,[35,36] and prediabetic men.[37] Increased inducible nitric oxide synthase (iNOS) and severe myocardial damage appeared in diabetic rats.[38]

**Bennefit Effects of Celery extract on Levels of serum Pancreas and liver damage in Diabetic Rats**

Previous studies had reported that hyperglycemia was correlated to chronic oxidative stress caused several organs damage. Alloxan induced reactive oxygen species which caused pancreas and liver damage. The complications that could be ameliorated by herbal antioxidants, such as: spirulina extract for treatment of liver injury,[39] ethyl vanillin isolated from vanilla beans decreased cell apoptosis in kidney,[40] and Myristica seed (nutmeg) extract alleviated decreased number of pancreatic islets.[41] The present study showed pancreas damage with severe decreased □eta-cells in islet Langerhans in diabetic rats. However, the rats in other groups that were given celery extract appeared with moderate to mild islet cells damage (Fig.1). The microscopic liver tissue showed more severe macrovesicular steatosis in diabetic rats compared to rats administered with the extract that appeared to have moderate to mild grade (Fig.2). The microscopic findings showed that celery extract might reduce pancreas and liver injury in diabetic rats mg. Higher dosage of celery extract (400 mg/KgBW/day) had better effects on amount number of normal cells in pancreas and liver tissue. It ameliorated the tissue injuries in the both organs.

**Bennefit Effects of Celery Extract on Serum Glucose, Trigliseride, Total Cholesterol, Aspartat amino transferase, and Alanine Transaminase**

Increased levels of serum glucose in diabetic rats caused by pancreas damage. Pancreas is the organ that synthesize and release insulin from islet Langerhans beta cells.[42] The hormone that increases glucose uptake by redistribution of glucose transporters 4 (GLUT4) to cell membranes.[43] Activity of insulin is also decreased by high level of plasma dipeptidyl peptidase 4 (DPP4). The enzyme that increased in fatty liver disease.[44] Serum levels of glucose, triglyceride, total cholesterol and alanine transaminase were the biochemical parameters that could be the markers of fibrosis in fatty liver.[45] Fatty liver was associated with oxidative stress. Serum levels of oxidized low density lipoprotein (ox-LDL) and lipid peroxide (malondialdehyde) increased in

patients with nonalcoholic steato-hepatitis (NASH).[46] Antioxidants could be protective against the complications caused by reactive oxygen species. A combination of Trigona, mellifera, and dorsata honey (Trihoney) increased the activity of antioxidants superoxide dismutase (SOD) and glutathione peroxidase (GPx) . It reduced levels of cholesterol serum and lowered progression of liver fibosis.[47] Reduced levels of antioxidant enzymes and increased reactive oxygen species caused pancreas damage followed by resistent to insulin. It caused hyperglicemia, hyperlipidemia, and liver tissue damage.[48]

The present study showed that the beneficial effects of celery extract on improved histologic findings in pancreas and liver were supported with lower serum levels of glucose (Fig.3),triglyceride (Fig.4), total cholesterol (Fig.5), and ALT (Table 1). Higher dose of celedry (400 mg/KgBW/day) did not have hypoglicemic effect. The levels of serum glucose and trigliceride did not lower in high dose of celery compared to low dose (200 mg/KgBW/day) in diabetic rats. However, the levels of serum total cholesterol and alanine transaminase decreased significantly on high dose of celedry administered to diabetic rats. The overall data provided to ascertain that celery extract alleviated the complications of diabetic rats.

## Conclusion

Celery extract administered to diabetic rats could show improvement in histopathological findings of pancreas and liver injury and serum levels of glucose, triglyceride, total cholesterol, and alanine transferase. It is recommended that celery extract might be a good supplement for diabetic pateints.

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## Authors' contributions

Andrew Johan:Conceptualization and drafted and reviewed the manuscript. Performed the statistical analysis and the preparation of tables and figures. Jodelin Muninggar: Performed sample preparation and animal handlings. Interpretation of data. Writing the full manuscript. All authors have read, reviewed, and approved the final manuscript

**Conflict of interest**

The authors declare no conflict of interest

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