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RESEARCH PAPER

Dietary fiber of jicama (*Pachyrhizus erosus* L., Fabaceae) tuber ameliorates kidney structure and function in mice fed with high-sucrose drink

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Abstract

Frequent consumption of high-sugar drinks (HSD) including sugar-sweetened beverages has been associated with the development of kidney disease. Otherwise, proper intake of dietary fiber extracted from the tuber of jicama (*Pachyrhizus erosus* L., Fabaceae) is shown to exert counteractive effects against HSD-induced metabolic syndrome including diabetes. However, it remains unelucidated whether the incorporation of jicama fiber in the diet could exert a beneficial effect on kidney function. This study aimed to elucidate the protective effect of jicama fiber in the diet against kidney disease caused by HSD. A total of thirty adult male albino mice were randomly assigned into three groups, the control group (fed with distilled water drink and standard diet), the high-sucrose drink group (HSD; fed with 30% sucrose solution drink and standard diet), and the high-sucrose drink + JF group (HSD + JF; fed with 30% sucrose drink and a standard diet supplemented with 25% of jicama fiber). The treatments were performed for ten weeks followed by the measurements of fasting blood glucose, plasma creatinine and kidney indices including urine protein, urine specific gravity, and refractive index and the examination of histopathological alterations in the kidney. The results demonstrated that the incorporation of JF in the diet at the dose of 25% could effectively counteract the elevation of fasting blood glucose and indicators of kidney damage including plasma creatinine, urine protein, urine specific gravity, and urine refractive index caused by HSD. However, JF failed to prevent HSD-induced mass reduction of the kidney but could ameliorate histopathological alterations in the kidney. Furthermore, JF effectively prevented tubular atrophy and fibrosis in the kidney in HSD-treated mice. Therefore, supplementation of the diet with JF at the dose of 25% could be effective in protecting the kidney against HSD. Thus, proper consumption of dietary fiber of jicama tuber has the potential to reduce HSD-induced kidney disease.

1. Introduction

Consumption of high-sugar drinks (HSD), especially sugar-sweetened beverages, has been associated with the development of various chronic diseases including kidney disease, one of the major health problems worldwide (Rebholz *et al*., 2019; Malik and Hu, 2022). However, the consumption rate of HSD is rapidly increasing not only in high-income countries but also in low and middle-income countries (Malik and Hu, 2022). As a result, the mortality rate due to kidney diseases is inevitably soaring globally while the use of chemically-synthesized drugs could lead to various adverse side effects in patients (Laville *et al*., 2020). Thus, the exploration of alternative natural remedies for kidney disease is urgently needed.

Vegetarian diets have been reported to negatively correlate with the prevalence of chronic kidney disease (CKD) (Chauveau *et al*., 2019). The beneficial effect of such a diet is suggested to be mediated by the high intake of dietary fiber. For instance, an experiment in diabetic mice demonstrated that a high-fiber diet is effective in precluding the development of diabetic nephropathy as indicated by less observable glomerular hypertrophy, fibrosis, albuminuria and podocyte injury (Li *et al*., 2020). An investigation by Mirmiran *et al*. (2018) revealed that high fiber intake, particularly from

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vegetables and legumes, reduced the risk of CKD in adult people. Moreover, a study in patients with advanced kidney disease showed that elevating the intake of fiber could improve the glomerular infiltration rate and counteract the rise of proinflammatory factors (interleukin-6, c-reactive peptides) without affecting the nutritional status (Lu *et al*., 2017). Another investigation revealed the effectiveness of increased daily fiber consumption in decreasing the level of serum uremic toxins including free indoxyl sulfate, free p-cresyl sulfate and indole acetic acids in children suffering from CKD (El-Amouri *et al*., 2021). Dietary fiber is thought to help treat CKD-related dysbiosis by promoting the growth of healthy gut microbiota, lowering levels of uremic toxins, oxidative stress, and inflammation, and decreasing the risk of these conditions (Su *et al*., 2021; Ranganathan and Anteyi, 2022). Therefore, proper intake of dietary fiber could exert preventive and therapeutic effects against kidney disease.

In previous reports, it has been demonstrated the effectiveness of dietary fiber extracted from tubers of the medicinal plant jicama (*Pachyrhizus erosus*). It was found that the incorporation of fiber into the diet could counteract the development of metabolic diseases including obesity and hyperglycemia (Santoso, Amelia and Rahayu, 2019) and non-alcoholic fatty liver disease (Santoso *et al*., 2019). However, it remains unknown whether the incorporation of the jicama fiber in the diet could also exert a protective effect on the kidney against the HSD challenge.

2. Materials and methods

2.1 Study design

This study had a double-blinded control design using 30 adult male mice (BALB/C strain; 2 months old, bodyweight 20-22 g) purchased from Wistar Company (a certified rodent Supplier for research, Yogyakarta, Indonesia). Before the experiment, mice were reared in the animal room with a regulated temperature, humidity and light-dark cycle (25.5-26.0°C; 66-67.5%; 12 hrs light/12 hrs dark, respectively), with each mouse per cage. During the 7-day- acclimatization period, all mice were fed with a standard diet (RATBIO, Citra Ina Fedmill, Jakarta, Indonesia) and distilled water *ad libitum*. Thereafter, mice were divided randomly into three different treatment groups (n = 10 for each group) as follows:

Group 1 (control): fed with distilled water drink + standard diet

Group 2 (HSD): fed with high-sucrose drink + standard diet

Group 3 (HSD + JF): fed with high-sucrose drink + standard diet combined with 25% jicama fiber (w/w).

The high-sucrose drink (HSD) was composed of 30% sucrose in distilled water. The dose of jicama fiber (25%) was referred to in the previous study (Santoso, Amelia and Rahayu, 2019) showing that 25% was the most effective dose in counteracting the detrimental effect of sugary diets. The diet treatment was performed for ten weeks continuously. The protocols for animal care and use of this study were in accordance with the regulations and guidelines of animal studies and have been approved by the Committee of Research Ethics Faculty of Medicine of Andalas University (No.528/ UN.16.2/ KEP-FK-2021).

2.2 Chemicals

Neutral buffered formalin was obtained from Delta laboratories (Jakarta, Indonesia), and pure sucrose and the chemicals for histopathological examination were purchased from Merck (Sigma Aldrich, Missouri, USA).

2.3 Jicama fiber extraction

The fiber extraction of the jicama tuber was carried out as per procedures previously described elsewhere (Kumalasari *et al*., 2014). The fresh tubers were harvested at five months old from a farm field in Kuranji, Padang, West Sumatra and immediately transferred to the lab. The species identity was validated by a certified plant taxonomist and the specimen was deposited in the Herbarium ANDA of Andalas University. The jicama tubers were washed with tap water and peeled, ground, and soaked in the distilled water for 12 hrs. The separated fiber was collected and steamed before being dried out in the oven at 69°C for 16 hrs. Eventually, the fiber was milled until fiber powder was achieved and then stored until use.

2.4 Measurements

2.4.1 Daily drink and food intake

During the latest week of treatment, food intake and drink intake were measured every day in the morning (07:30 A.M.) using a sensitive digital balance.

2.4.2 Bodyweight and blood glucose

The body weight of mice was measured at the end of treatment using a digital balance (SF-400C, Zhezhong Weighing Apparatus Factory, China). Moreover, fasting blood glucose was also determined at the end of treatment after 18 hrs of fasting using a glucometer (AGM-4000Allmedicus, South Korea).

2.4.3 Urine indices

Urine samples were collected in the morning (at 9:30

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AM) on the latest day of treatment. Every single mouse was placed on a sterilized transparent plastic sheet (30 × 30 cm; WLS-PET SHEET01, Shanghai Wallis Technology Co. ltd., China) until it urinated. The fresh urine was immediately collected using a micropipette immediately transferred into a microtube and stored at 4°C until use for measurement. Urine protein level was determined by using an automated laboratory urine analyzer (YSU-BC 400, Guangzhou, China). Urine-specific gravity and refractive index were measured using a refractometer (The Schuco Clinical Refractometer Model 5711-2021, NY, USA).

2.4.4 Plasma creatinine

At the end of treatment, animals were sacrificed by dislocating cervical vertebrae and the blood sample was immediately collected from the heart. Subsequently, blood was centrifuged at 10,000 rpm for 10 mins at 4°C and the plasma sample was subjected to creatinine measurement by using creatinine (serum) colorimetric assay kit (No. 700460 Cayman Chemicals, Michigan, USA). The procedures of measurement were as per the protocol described by the product manufacturer.

2.4.5 Histopathological examination of the kidney

Upon blood sample collection, mice were dissected and the kidneys were removed, weighed then fixed in 10% buffered neutral formalin solution for 18 hrs. Then, the tissue processing procedures and hematoxylin-eosin staining were carried out for every single left kidney following the protocols as previously described (Cardiff *et al*., 2014). Each representative tissue slide (four slides with five fields of view) was examined under a microscope (CX31 Olympus, Tokyo, Japan) and the pathological alterations were recorded including the incidence of tubular atrophy and fibrosis.

2.5 Statistical analysis

The quantitative data were presented as mean ± standard deviation (SD) and the statistical differences among groups were justified using ANOVA followed by the Bonferroni posthoc test with P-value < 0.05 was considered significant.

3. Results

3.1 Effect of Jicama fiber on drink and food intakes, body weight and blood glucose

The daily drink intake showed no significant difference among all groups of treatment (Figure 1A). However, the daily food intake was significantly lower in the HSD and HSD + JF groups as compared with the control group (P<0.05; Figure 1B). The body weight was significantly higher in the HSD group as compared to the control group, but it was comparable between HSD and HSD + JF groups (*P*>0.05; Figure 1C). The fasting blood glucose was markedly increased in the HSD group as compared with the control and HSD + JF groups (*P*<0.01; Figure 1D).

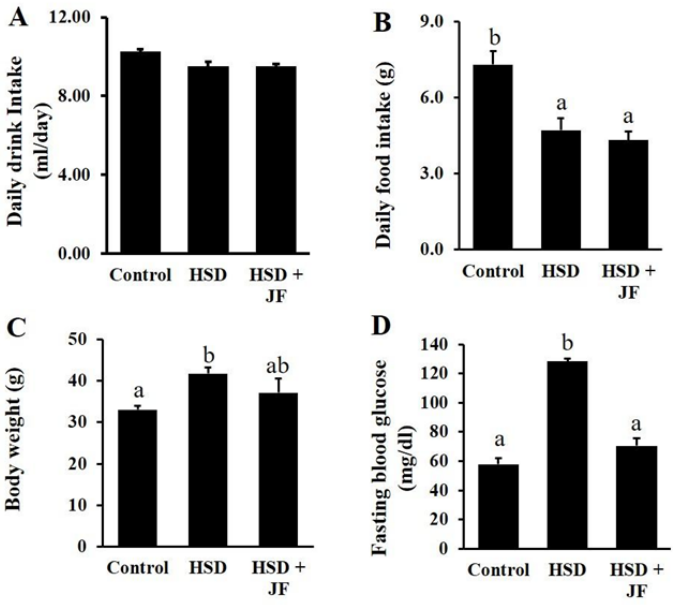

Figure 1. Effect of jicama fiber supplementation on drink and food intake, body weight and fasting blood glucose. (A) Daily liquid intake as measured at the latest week of treatment, (B) daily food intake as measured at the latest week of treatment, (C) final body weight, (D) fasting plasma glucose determined at the end of the experiment. Different lower-case characters above the bars indicate statistical differences (*P*<0.05). n= 8. HSD (high-sucrose drink), JF (jicama fiber).

3.2 Effect of Jicama fiber on indicators of kidney function

After ten weeks of treatment, plasma creatinine was markedly elevated in the HSD group as compared with other groups (P<0.01; Figure 2A). Similarly, levels of urine protein, urine specific gravity and urine refractive index were significantly higher in the HSD group (P<0.01; P<0.05, respectively) as compared to control and HSD + JF groups.

3.3 Effect of Jicama fiber on kidney structure

Measurement of kidney mass showed no difference in kidney weight among all groups (P>0.05; Figure 3A), but kidney index was significantly lower in the HSD and HSD + JF groups as compared with the control group (P<0.05; Figure 3B). Histological examination of the kidney revealed severe damage in the glomerulus (glomerulosclerosis) and tubules in the HSD group, but not in the control group (Figure 4A-B). However, such damages were less observable in the HSD + JF group (Figure 4C). The incidence of tubular atrophy was markedly higher in the HSD group as compared with other groups (P<0.01; Figure 5A). Likewise, the

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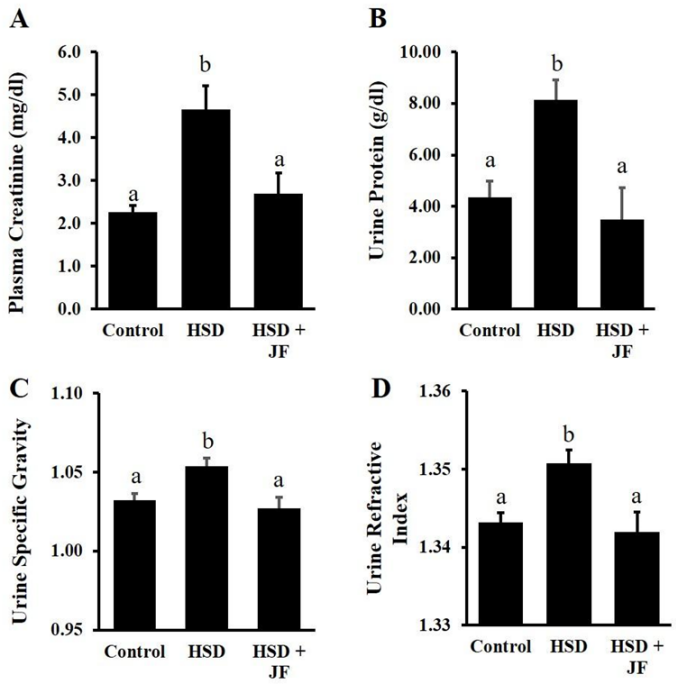

Figure 2. Effect of jicama fiber supplementation on indicators of kidney function. (A) Level of creatinine in the blood, (B) protein in the urine, and (C) urine specific gravity, (D) urine refractive index as determined after ten weeks of treatment. Different lower-case characters above the bars indicate statistical differences (P<0.05). n = 8. HSD (high-sucrose drink), JF (jicama fiber).

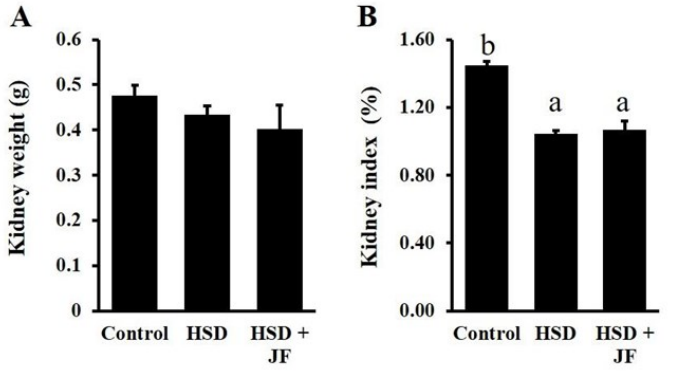

Figure 3. Effect of jicama fiber supplementation on kidney weight. (A) kidney weight and (B) kidney index of mice after ten weeks of treatment. Different lower-case characters above the bars indicate statistical differences (P<0.05). n = 8. HSD (high-sucrose drink), JF (jicama fiber).

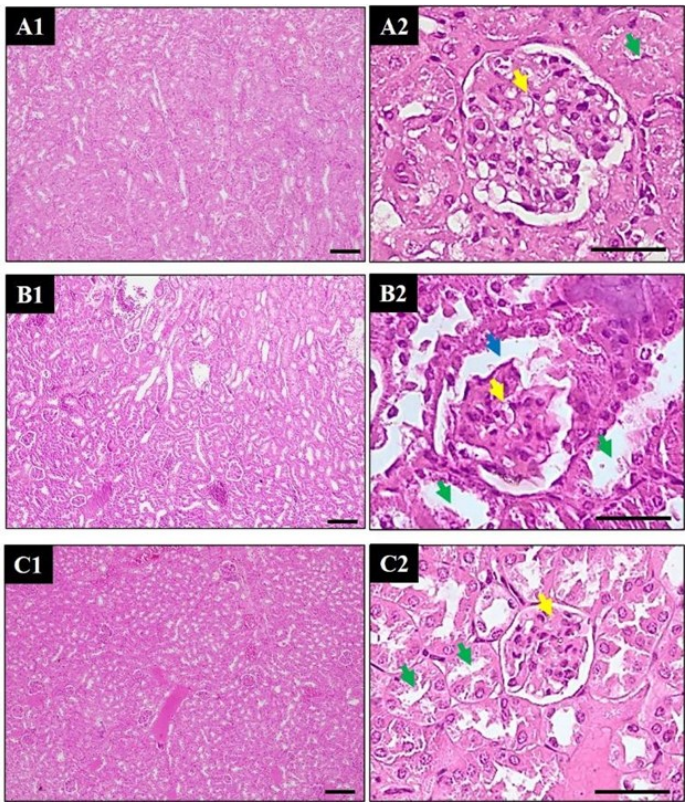

Figure 4. Effect of jicama fiber supplementation on the histopathological alterations of the kidney. Photomicrograph of the kidney histology stained with hematoxylin-eosin. Left panels: lower magnification, right panels: higher magnification. (A1-A2) Control group, (B1-B2) HSD group, (C1-C2) JF group. HSD (high-sucrose drink), JF (jicama fiber). Green arrows indicate tubules, yellow arrows indicate glomerulus, blue arrow indicates glomerular damage. n = 8. Scale bars in left panels: 60 µm, right panels: 20 µm.

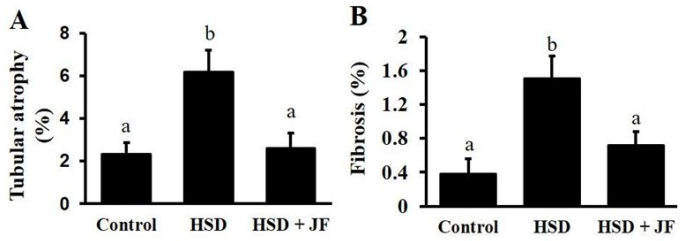

Figure 5. Effect of jicama fiber supplementation on the Incidence of tubular atrophy and fibrosis in the kidney. Different lower-case characters above the bars indicate statistical differences (P<0.05). n = 8. HSD (high-sucrose drink), JF (jicama fiber).

incidence of fibrosis was significantly higher in the HSD group as compared with the control and HSD + JF groups (P<0.01; Figure 5B).

4. Discussion

This present study demonstrated the effectiveness of JF in preventing kidney damage caused by HSD. The incorporation of JF at the dose of 25% in the diet could effectively preclude the occurrence of some indicators of kidney disease including structural and functional impairments in the kidney.

A meta-analysis study has indicated an association between frequent consumption of sugary beverages and the development of kidney disease (Lo *et al*., 2021). It has been reported that HSD could cause hyperglycemia (Graneri *et al*., 2021). As also commonly observed in diabetic patients, hyperglycemia could promote severe microvascular damage in the kidney thereby reducing kidney function (Gil *et al*., 2020). Hyperglycemia could also induce the development of kidney disease through the mechanisms involving dysregulation of metabolic factors (hormones, blood glucose, plasma lipids), hemodynamic disturbances, and oxidative stress (Rayego

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-Mateos *et al*., 2020). Such disturbances subsequently promote damage to endothelial, mesangial, podocytes and tubular cells of the kidney. On the other hand, sustaining blood glucose at normal levels has been recommended to preclude kidney damage (Garla *et al*., 2019). This current study revealed that JF was capable of sustaining a normoglycemic state in HSD-fed mice as indicated by significantly lower fasting blood glucose after ten weeks of treatment. Thus, the renoprotective effect of JF, as presently revealed, might be mediated by its blood glucose-lowering effect. JF may improve blood glucose profiles, especially fasting blood sugar levels, in part by shielding pancreatic tissue from degeneration and ectopic fat buildup caused by high-sugar diets (Santoso *et al*., 2020). JF may also lessen glucose absorption in the colon, lowering the amount of glucose that enters the circulatory system thereby mitigating hyperglycemia.

This study also found that mice treated with HSD exhibited proteinuria, glomerulosclerosis, tubular atrophy and fibrosis. Moreover, the creatine accumulation in the blood plasma, the urine specific gravity and urine refractive index were markedly elevated, suggesting an impaired glomerular function. In contrast, the supplementation of dietary fiber from jicama tuber improved kidney function as particularly indicated by lower plasma creatinine and urine protein levels. This finding is in line with the previous study showing that increased fiber intake in individuals with CKD could reduce the level of plasma creatinine as well as improve the filtration rate of the glomerulus (Salmean *et al*., 2013). Another study also revealed that dietary fiber intake could effectively lower the urea and creatinine levels in the plasma of people with CKD (Chiavaroli *et al*., 2015). In addition, a previous review also suggested the potential of fermentable dietary fibers to improve kidney function (Kieffer *et al*., 2016).

In addition to the blood-glucose lowering process, another plausible mechanism of JF to improve kidney function is by elevating the microbial fermentative activity and its subsequent beneficial products in the gastrointestinal tract. The fermentable fibers serve as a substrate for the microbiota in the gut and subsequently increase their activity and population, particularly those associated with health-promoting effects (Fan and Pedersen, 2021). A study demonstrated that an increase in fiber-fermentator gut microbiota could lead to the alteration of production/utilization of microbial derived xeno-metabolites (phenol and p-cresol) and urea (Kieffer *et al*., 2016). Such implications lead to subsequent multiple beneficial consequences including decreased caecal pH and improved gut barrier function thereby decreasing inflammatory responses in the kidney (Kieffer *et al*., 2016). The fermentative activity of the gut microbiota produces short-chain fatty acids (SCFAs) including acetate, propionate and butyrate (Chen *et al*., 2019). Moreover, an increase in SCFA production has been suggested to be closely associated with the improvement of kidney function (Al-Khodor and Shatat, 2017; Felizardo *et al*., 2019). Both dietary fiber supplementation and direct SCFA administration are effective in alleviating acute kidney injury in mice (Liu *et al*., 2021). Likewise, the elimination of SCFA receptors such as G-coupled protein receptors (GPR41 and GPR109A) diminish the protective effect of SCFA against kidney injury (Li *et al*., 2020), suggesting the pivotal role of SCFA through its receptors in mediating the beneficial effect of fiber against kidney disease. Taken together, the findings indicate that the renoprotective effect of fiber against renopathy is mediated through gut microbiota modulation, particularly SCFA-producing microbes. Accordingly, it is also speculated that the renoprotective effect of JF against HSD might be mediated by the modulation of gut microbiota composition as well as the elevation of SCFA production. However, in this present study, neither gut microbiota composition nor the SCFA level was determined. Thus, further study is needed to confirm it.

Despite its beneficial effects in sustaining better kidney functions under HSD treatment, JF at the dose of 25% failed to preclude an apparent reduction in kidney index (a ratio of kidney weight and body weight). This discrepancy may indicate that the structural degeneration of the kidney caused by HSD was not fully precluded by the JF. As a result, the mass of kidney tissues is reduced while body weight increases thereby reducing kidney index. Alternatively, the degeneration of kidney tissue caused by HSD treatment requires a longer period to be fully recovered under JF treatment. Thus, further study with a prolonged duration of JF treatment (more than ten weeks) is needed to determine it.

In addition, this present study found that mice fed with HSD and HSD + 25% JF had a significantly lower food intake as compared with those fed ND. It was suggested that such reduction might be due to the achieved satiety state upon HSD consumption. The satiety involving neural circuits controlling feeding in the hypothalamus (including those involving neuropeptide Y, proopiomelanocortin, and oxytocin and nesfatin-1 neurons) are known to be sensitive to blood glucose elevation (Horvath and Diano, 2004). Consequently, the higher the glucose intake (from HSD), the faster the satiety state is achieved thus reducing subsequent food intake.

In this current investigation, it was discovered that mice in the HSD-fed group had significantly lower food

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intake than mice in the control group, although having significantly larger body weights. The difference in body weight might be associated with the difference in total energy intake. Mice in the control group and HSD group were being fed identical solid food (standard chow diet). However, mice in the HSD group drank a high-energy liquid with 30% sucrose at the same time as mice in the control group drank distilled water (zero energy content). As a result, HSD mice consumed more total calories than mice in the control group, resulting in increased body weight. According to a study by Togo *et al*. (2019), mice who consumed liquid sucrose had increased calorie intake and body weight gain, which led to obesity and related metabolic problems. Additionally, earlier research showed that consuming HSD led to a significant rise in the mass of white adipose tissue, which promoted uncontrollable weight gain (Santoso *et al*., 2020).

There are some limitations that should be considered. Firstly, the levels of SCFAs under the treatment of JF were not determined. As a result, it remains unknown whether the protective effect of JF on kidney against HSD is mediated by the action of SCFAs. Secondly, whether JF could also exert a therapeutic effect against HSD was not investigated. Thirdly, it is also undetermined whether the higher or lower dose of JF (than 25%) in the diet will exert similar beneficial effects against HSD.

5. Conclusion

The incorporation of the JF at the dose of 25% in the diet is effective in preventing the development of kidney disease caused by the overconsumption of sugary drinks in mice. Hence, JF could be considered as an alternative supplement for preventing the development of kidney disease.

Conflicts of interest

The authors have none to declare

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