TRENDS IN SCIENCES 2025; 22(12): 11224
https://doi.org/10.48048/tis.2025.11224 RESEARCH ARTICLE

SGLT2 Downregulation Mediates the Antidiabetic and Renoprotective Effects of *Swietenia Macrophylla* King in A Neonatal Streptozotocin-Induced Rat Model

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Received: 9 July 2025, Revised: 18 July 2025, Accepted: 25 July 2025, Published: 20 September 2025

Abstract

Swietenia macrophylla King (SMK) has been reported to exhibit hypoglycemic activity by lowering blood glucose levels, which may aid the management of diabetes mellitus. Elevated blood glucose leads to increased glucose reabsorption in the kidneys and potentially serious kidney complications. In this study, 24 neonatal Wistar rats were induced with 90 mg/kgBW Streptozotocin (STZ) on the 2nd day of birth and divided into 6 groups: Normal control, negative control, positive control, and 3 groups were given *Swietenia macrophylla* King extract at doses of 25, 50 and 100 mg/kgBW for 21 days. Blood glucose, urine glucose, and Sodium Glucose Cotransporter 2 (SGLT2) expression were examined as biomarkers of glucose reabsorption, and histopathology of the kidney was assessed to evaluate tubular injury in this study. Blood glucose levels and SGLT2 expression in the group receiving extract were lower than the negative control group ($p \leq 0.005$). The histopathological picture of the tubular injury in the group that received the extract showed less damage than the negative control group ($p \leq 0.001$). The urine glucose levels in the groups that received the extract decreased compared to the first measurements ($p < 0.05$). The findings indicate that *Swietenia macrophylla* King extract possesses significant antidiabetic and renoprotective properties, as evidenced by reduced blood and urinary glucose levels, decreased SGLT2 expression, and improved renal histology. These results suggest its potential as a promising natural therapeutic agent for diabetes management, warranting further investigation to explore its underlying mechanisms and clinical applicability.

Keywords: Diabetes mellitus, *Swietenia macrophylla* King, Renoprotective, SGLT2, Blood glucose, Tubular injury, Urine glucose

Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia due to abnormalities in insulin secretion, insulin action, or both [1]. In 2021, Indonesia ranked as the country with the fifth-largest number of diabetes patients worldwide, with approximately 19.5 million Indonesians aged 20 - 79 years affected by the disease [2]. Persistent hyperglycemia in diabetes often leads to kidney damage, making diabetic nephropathy one of the most serious long-term complications. The prevalence of diabetes mellitus continues to rise, with high incidence and mortality rates, involving pancreatic endocrine hormones such as insulin and glucagon. Its main manifestations include disturbances in lipid, carbohydrate, and protein metabolism, ultimately leading to hyperglycemia [3,4]. Under normal physiological conditions, glucose serves as the primary energy source through carbohydrate metabolism, regulated by insulin produced by pancreatic β-cells, thereby maintaining blood glucose levels. However, in diabetes mellitus, this regulation is impaired due to insulin deficiency or reduced cellular sensitivity to

insulin, resulting in persistent hyperglycemia [5]. Chronic hyperglycemia may progress to diabetes mellitus with various complications [4]. One of the major complications of diabetes mellitus is kidney damage, often indicated by tubular injury [6]. Elevated blood glucose levels in diabetes are also associated with increased expression of Sodium-Glucose Co-Transporter 2 (SGLT2) [7]. SGLT2 is a glucose transporter located in the proximal renal tubules and is responsible for approximately 90% of glucose reabsorption [8]. Several drugs have been developed as SGLT2 inhibitors, including dapagliflozin, which is approved for clinical use in Indonesia. These drugs work by inhibiting glucose reabsorption in the renal tubules via SGLT2 receptors. Inhibiting this transporter reduces blood glucose levels by promoting glucose excretion through urine (glucosuria), with efficacy dependent on glucose concentration [9]. Due to its major role in glucose reabsorption, SGLT2 is considered an ideal target for diabetes treatment [10]. The efficacy and safety of antidiabetic drugs require preclinical trials using animal models. Hyperglycemic animal models of diabetes are commonly induced using compounds such as alloxan or streptozotocin (STZ), which damage the pancreatic β-cells of Langerhans, effectively mimicking both type 1 and type 2 diabetes mellitus [11-13]. One of the plants with potential to be developed as a medicinal plant in Indonesia is *Swietenia macrophylla* King (SMK), which has been used in traditional medicine to treat diabetes, hypertension, and malaria in Indonesia [14]. Almost all parts of the *Swietenia macrophylla* King plant can be used as traditional medicine to treat various human diseases. The seeds of the *Swietenia macrophylla* King can be significantly used for medicinal purposes. *Swietenia macrophylla* King seed extract, reported by researchers, has antidiabetic pharmacological effects capable of lowering blood glucose levels [15]. However, there is limited research on the effects of SMK extract on kidney tissue in the context of diabetes mellitus. While previous studies have investigated the hypoglycemic effects of *Swietenia macrophylla* King, the specific involvement of renal glucose transporters, particularly SGLT2, has not been established, especially in a neonatal model that mimics early-onset diabetes. This study aims to investigate the antihyperglycemic and renoprotective effects of *Swietenia macrophylla* King seed extract, focusing on its impact on renal structures in a neonatal streptozotocin-induced diabetic rat model. The findings are expected to provide insights into the pathophysiology of diabetic nephropathy and explore the therapeutic potential of SMK extract.

Materials and methods

Experimental design

A pre-test and post-test control group design was used with 24 male Wistar rats, with the sample size determined by Federer's formula (n-1) (t-1) = 15, where n = is the sample size per group and t = is the number of groups. The animals were randomly allocated into 6 groups (n = 4 per group): untreated control, negative control (0.5% Na-CMC), positive control (Dapagliflozin 0.9 mg/kgBW), and the 3 treatment groups receiving *Swietenia macrophylla* King extract at 25, 50, and 100 mg/kgBW (SMK25, SMK50, SMK100). The study was approved by the Medical and Health Research Ethics Committee (MHREC) (KE/FK/1482/EC/2023) and conducted at the Faculty of Medicine, Universitas Gadjah Mada.

Experimental animal model

Neonatal Wistar strain rats were induced using a streptozotocin (Cayman Chemical Co.) solution at a dose of 90 mg/kgBW administered intraperitoneally. Streptozotocin is immediately dissolved in a cold 0.1 M citrate buffer with a pH of 4.5 before injection. Streptozotocin is given only once at 2 days of age, then after 4 weeks, the baby is weaned from its mother.

In this study, we use male rats for the experiment. The condition of the diabetic rats was observed by measuring their fasting blood glucose levels at 8 weeks of age. Rats are hyperglycemic if their fasting blood glucose levels exceed 1.5 times the normal group (> 112 mg/dL in this study) [16].

Preparation of *Swietenia macrophylla* king extract

Swietenia macrophylla King extract was given in 3 doses dissolved in 0.5% Na-CMC solution and given orally through a gastric tube for 21 days with a 2 - 5 mL volume. The selected doses of 25, 50 and 100 mg/kgBW for *Swietenia macrophylla* King extract were chosen within the effective range reported in previous *in vivo* studies on *Swietenia macrophylla* and similar medicinal

plants, which demonstrated significant antihyperglycemic effects and safety at doses ranging from 20 to 300 mg/kgBW [17,18]. These dose levels were also supported by preliminary in-house observations indicating antihyperglycemic activity without signs of toxicity (data not shown).

This study used SMK extract produced in tablet form by PT. Deltomed Laboratories follows Good Manufacturing Practices. The extraction process was done using the percolation method by chopping dried SMK seeds with a crusher machine and then placing them into a 100 kg percolator. Seventy percent of ethanol was added to the percolator machine, and percolation was conducted for 3 h. The resulting percolate was then separated and evaporated to remove the ethanol solvent. The thick extract of SMK obtained is then mixed with drying agent maltodextrin and cabosil, and subsequently dried using the spray drying method to form a powder. The dry powder containing SMK extract is then formed into tablet preparations.

Preparation of 0.5% Na-CMC

The Na-CMC (sodium carboxymethyl cellulose) solution was administered to the negative control group to compare the presence or absence of effects against the positive control and the testing extract. The use of Na-CMC suspension as a negative control is because it is a carrier of test material that has inert properties, so that it does not affect the activity of the active substance and is expected not to influence the reading of the test parameter values [19]. The 0.5% Na-CMC is prepared by weighing approximately 500 mg of Na-CMC, dissolving it in some warm distilled water, then stirring, and adding more distilled water while continuing to stir. After dissolving, the remaining distilled water was added until a Na-CMC solution volume of 100 mL was obtained.

Preparation of dapagliflozin

Dapagliflozin was given to the positive control group. Dapagliflozin is one of the SGLT2 Inhibitors used to treat diabetes mellitus. The maximum dose of Dapagliflozin used in humans is 10 mg [20]. Dose conversion is performed to determine the dosage for test animals, which is 0.9 mg/kgBW. Dapagliflozin dissolved in 0.5% Na-CMC and was administered orally for 21 days using a gastric tube at a 2 - 5 mL dose.

Blood glucose level measurement

Blood glucose levels were measured on day 0 (before treatment) and days 7, 14, and 21 (after treatment) using blood samples (1 - 1.5 mL) collected from the retro-orbital plexus of rats in each group. Blood sampling was performed after the rats were fasted for 10 - 14 h. Blood is collected in a microtube, left to stand for 30 min at room temperature, centrifuged at 3,600 rpm for 10 min, and then the supernatant is taken for measurement. Blood glucose level examination is performed using the enzymatic colorimetric test GOD-PAP method, with a microplate. The Colorimetric Test GOD-PAP method involves mixing 2 µL of serum/sample/blank with 200 µL of GOD-PAP reagent (Glucose GOD FS, DiaSys, Germany) and incubating it for 20 min at room temperature. Results were read using a spectrophotometer at a wavelength of 490 nm. The glucose levels in each group are expressed in mg/dL and calculated based on the absorbance obtained using the following formula:

$$\text{Glucose level} = \frac{\text{Absorbance Assay} - \text{Blank}}{\text{Absorbance Standar} - \text{Blank}} \times \text{Standard glucose level } (100 {}^{mg}/_{dL})$$

Measurement of urine glucose levels

The measurement of urine glucose levels was taken on day 0 (before treatment), days 7, 14 and 21 (after treatment). The sample used was urine from rats that had been collected through a metabolic cage, totaling 1.5 mL, after being fasted for 10 - 14 h. The glucose level is measured using the Cobas 111 analyzer (Roche Diagnostic Co.) The results of the urine glucose level measurement are presented as a percentage change.

Animal termination

Euthanasia is performed on all rats after the study. The anesthetic drug used for the euthanasia of test animals at the end of the study is (a combination of 500 mg ketamine and 50 mg/kgBW xylazine intraperitoneally). To ensure that the animals are no longer alive, all sacrificed animals are observed for signs of death, including loss of heartbeat (palpation), loss of pupil reflex to light, and loss of breath (observation of abdominal breathing movements). The

animals are sacrificed, and the organs needed for the research are taken and placed in a fixative solution.

Expression of sodium-glucose co-transporter 2

The evaluation of SGLT2 expression in this study used the Immunohistochemistry (IHC) method on kidney preparations in each group using the SGLT2 polyclonal antibody (Elabscience, China E-AB-12475). Field-of-view images were taken using a Sinher microscope. The samples and IHC method were prepared at the Anatomical Pathology Laboratory of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia. The examination of SGLT2 expression levels was conducted qualitatively by observing the increased staining of the apical border in the proximal tubule epithelium. Quantitative analysis was conducted by calculating the percentage of the positively stained area fraction using the ImageJ application.

Renal histopathology

Proximal tubular injury was evaluated on PAS-stained kidney sections under a binocular microscope at 640× magnification across 10 random fields per sample. Injury features included inflammatory areas, brush border loss, intraluminal casts, lumen dilation, and epithelial cell thinning. Scoring was semi-quantitative on a 0 - 3 scale: 0 = normal, 1 = focal damage, 2 = multifocal damage, and 3 = diffuse damage. Two independent observers, blinded to treatment allocation, performed the scoring. Interobserver variability was minimized by prior calibration of scoring criteria and resolved by consensus in case of discrepancies.

Statistical analysis

The measurement results on the experimental animals were recorded, tabulated, and statistically analyzed using the IBM SPSS Statistics with a 95% confidence interval and a significance level of 0.05 (p = 0.05). For each parameter, a normality data analysis was conducted using the Shapiro-Wilk normality test and the homogeneity test (Levene Test) with a p-value > 0.05. If the data is normally distributed and homogeneous, a one-way ANOVA parametric test follows it, then a Post-Hoc LSD analysis is conducted to see the differences between treatment groups. If the data is not normally distributed and homogeneous, it is followed by a Kruskal-Wallis non-parametric test, then a Post-Hoc Mann-Whitney analysis.

Results and discussion

Blood glucose levels

Table 1 presents the average fasting blood glucose levels of each group, showing significant reductions in the SMK-treated and positive control groups compared to the negative control group on day 7 ($p < 0.05$). On day 14, although the same groups exhibited lower glucose levels than the negative control group, the differences were not statistically significant ($p > 0.05$). However, the SMK50 group showed significantly lower glucose levels compared to the negative control group (p = 0.041).

On day 21, the Swietenia macrophylla King treatment group, control group, and positive control group again demonstrated lower glucose levels than the negative control group. However, these differences were also not statistically significant ($p > 0.05$). Overall, fasting blood glucose levels in the treatment group decreased over time following the administration of SMK extract.

Notably, the extract significantly reduced fasting blood glucose levels by day 7 when compared to the negative control group. After 21 days of administration, the SMK extract tablet continued to gradually reduce fasting blood glucose levels. However, by days 14 and 21, these reductions were not statistically significant relative to the negative control group. This lack of significance is likely due to a natural decline in blood glucose levels in the negative control group, although they remained within hyperglycemic ranges throughout the study.

Table 1 Average fasting blood glucose levels of rats in each group.

Group and dose $n = 4$	Blood glucose levels (mg/dL)			
	Mean ± SD			
	Day 0	Day 7	Day 14	Day 21
Control	73.99 ± 11.61	70.20 ± 18.77*	89.95 ± 23.87	73.82 ± 15.03
Negative control	253.81 ± 50.37[a]	239.50 ± 37.76	166.53 ± 62.96	112.42 ± 38.93
Positive control	255.54 ± 37.82[a]	139.90 ± 51.87*[#]	140.47 ± 36.4[#]	110.79 ± 39.71[#]
SMK25	210.64 ± 44.91[a]	182.57 ± 28.65*[#]	112.22 ± 75.39	111.39 ± 64.78
SMK50	202.84 ± 6.92[a]	196.39 ± 18.2*[#]	81.87 ± 18.76*[#]	80.55 ± 14.13[#]
SMK100	208.13 ± 94.83[a]	120.37 ± 62.7*	116.63 ± 77.14	115.91 ± 47.26

a, significantly different compared to control ($p < 0.05$); *, significantly different compared to negative ($p < 0.05$); #, significantly different compared to day 0 in each group ($p < 0.05$, Post-Hoc LSD analysis)

Neonatal administration of streptozotocin (STZ), as described by Bonner-Weir *et al*. [21] induces acute damage to pancreatic β-cells, followed by spontaneous regeneration and transient normalization of blood glucose levels within approximately 2 weeks. Previous studies have shown that *Swietenia macrophylla* King extract activates the glucokinase enzyme, which plays a critical role in lowering blood glucose levels. In addition to its antihyperglycemic effect, the extract also exhibits antioxidant properties [22,23]. Antioxidants function by neutralizing free radicals, thereby preventing cellular damage caused by oxidative stress. This protective mechanism may support the regeneration of pancreatic tissue, enhance insulin production, improve cellular glucose uptake, and ultimately contribute to reduced blood glucose levels [24].

The antihyperglycemic effects observed in our study are consistent with prior findings on plant-based therapies for diabetes. *Momordica charantia* (bitter melon) has been shown in animal models to significantly lower blood glucose levels by enhancing insulin sensitivity, stimulating β-cell function, and activating pathways such as AMP-activated protein kinase (AMPK) and PPARγ, which is comparable to the effects of conventional antidiabetic drugs [25]. Similarly, *Andrographis paniculata* (sambiloto) has demonstrated glucose-lowering activity *in vivo* by upregulating GLUT-4 expression and improving insulin sensitivity in Wistar rats [26]. In addition to glycemic control, these plants have also shown renoprotective properties in diabetic models, reducing oxidative stress and improving kidney structure [25,26].

In contrast, our findings with *Swietenia macrophylla* King not only confirm its antihyperglycemic and renoprotective effects but also reveal significant downregulation of renal SGLT2 expression, a mechanism less commonly reported in herbal antidiabetic interventions. This suggests that SMK may provide an additional therapeutic pathway by targeting renal glucose reabsorption, beyond the insulin-centric actions typically associated with most plant extracts.

Urine glucose levels

The percentage changes in urinary glucose levels for each group are presented in **Table 2**. Based on the Mann–Whitney post hoc test, a significant decrease in urinary glucose levels was observed on days 7 and 21 in both the control and SMK treatment groups compared to day 0 ($p < 0.005$). In the negative control group, a significant decrease was observed only on day 21, while the change on day 7 was not statistically significant ($p > 0.005$).

On day 14, urinary glucose levels significantly decreased in the control group, negative control group, SMK25, and SMK50 groups compared to day 0 ($p < 0.005$). In contrast, the SMK100 group showed a decrease that was not statistically significant ($p = 0.131$). In contrast, the positive control group (treated with Dapagliflozin) showed a statistically significant increase in urinary glucose levels on days 7, 14, and 21 compared to day 0 ($p = 0.014$), with a peak increase of 99.2% on day 21. The SMK-treated groups demonstrated a consistent and statistically significant

reduction in urinary glucose levels across all time points compared to baseline. The greatest reduction occurred on day 21. This trend suggests that SMK extract may improve glucose regulation and renal glucose excretion.

Table 2 Average percentage change in urine glucose levels in each group.

Group and dose	**Average percentage change in urine glucose levels**			
***n* = 4**	**Day 0**	**Day 7**	**Day 14**	**Day 21**
Control	100%	–17.3 %*	–65.6 %*	–54.8 %*
Negative control	100%	–76.1 %	–85.3 %*	–95.7 %*
Positive control	100%	+69.6 %*	+59.3 %*	+99.2 %*
SMK25	100%	–93.3 %*	–81.8 %*	–98.2 %*
SMK50	100%	–79.0 %*	–63.3 %*	–95.4 %*
SMK100	100%	–58.6 %*	–68.5 %	–86.6 %*

*, significantly different compared to day 0 in each group ($p < 0.05$, Post-Hoc Mann-Whitney analysis); –, decrease; +, increase.

The purpose of measuring urinary glucose levels in this study was to evaluate whether *Swietenia macrophylla* King (SMK) exhibits a mechanism similar to that of SGLT2 inhibitors. Interestingly, while dapagliflozin increased urinary glucose excretion, consistent with its mechanism of inhibiting SGLT2-mediated glucose reabsorption, SMK extract resulted in decreased urinary glucose levels despite significant SGLT2 downregulation. This apparent discrepancy suggests that the predominant effect of SMK is improved blood glucose control rather than direct enhancement of glucosuria. Previous research has shown that *Swietenia macrophylla* seed extract reduces blood glucose levels by stimulating pancreatic β-cell regeneration, enhancing insulin secretion through antioxidant mechanisms, and activating glucokinase to promote glucose utilization [22].

Through these actions, the extract likely lowers plasma glucose concentration, reducing the filtered glucose load presented to the renal tubules and consequently decreasing urinary glucose excretion, even with reduced SGLT2 expression. This mechanism differs from classical SGLT2 inhibitors and highlights the multifactorial antidiabetic effects of SMK. Furthermore, SMK extract appears to contribute to renal functional stability and renoprotection, likely through reducing hyperglycemic burden and oxidative stress rather than by promoting glucose reabsorption. These combined effects underscore its potential as a plant-based therapy for diabetic nephropathy. Further studies isolating renal effects from systemic glucose control are needed to confirm the contribution of SGLT2 modulation to its overall pharmacological profile.

Sodium glucose co-transporter 2 (SGLT2) expression

As shown in **Figure 1**, it can be seen that SGLT2 is expressed in the proximal tubules located in the renal cortex, indicated by the orange-brown color. Quantitative analysis was conducted by calculating the percentage of positively stained area fractions from 10 different fields of view using the Image-J application. The One-way ANOVA test and post-hoc LSD test results indicated a statistically significant difference between each group in the SGLT2 area fraction percentage results, with a p-value < 0.05.

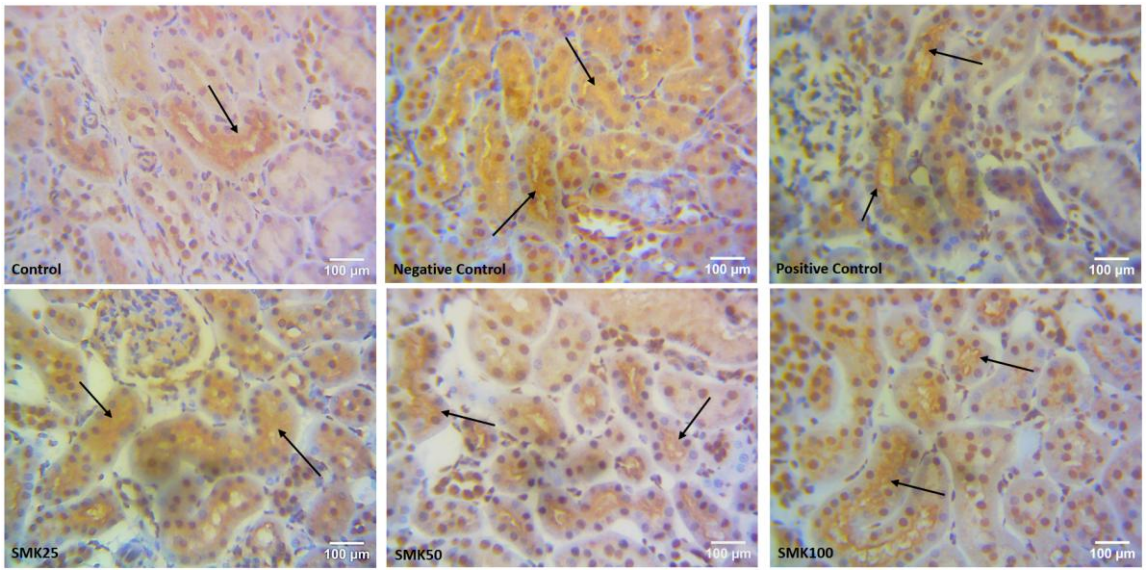

Figure 1 Microscopic appearance of the kidney showing SGLT2 expression in proximal tubules (immunohistochemistry staining, 640× magnification). Black arrows indicate areas of positive SGLT2 staining (brown color). SMK-treated groups show reduced expression compared to the negative control. Scale bar = 100 µm.

The area fraction percentage of SGLT2 expression in the SMK group, positive control group, and normal control group was significantly lower than that in the negative control group, with a p-value < 0.05 (**Figure 2**). Although preclinical research on the effects of *Swietenia macrophylla* King seed extract remains limited, this study demonstrates that SGLT2 expression in the group treated with the extract was significantly reduced compared to the negative control group.

Supporting this finding, an *in silico* study by Vigneshwaran and Lalitha evaluated antidiabetic compounds isolated from *Swietenia macrophylla* King seeds using molecular docking analysis targeting the SGLT2 protein. The analysis revealed that swietenine, swietenolide, mahonin, and swietemahonolide potentially act as SGLT2 inhibitors, suggesting the involvement of these compounds in modulating renal glucose transport [27].

However, the precise mechanistic link between these bioactive compounds and SGLT2 downregulation remains unclear. While molecular docking provides supportive evidence, it does not confirm biological activity *in vivo*. The observed effect could involve additional regulatory pathways affecting SGLT2 expression at the transcriptional or post-transcriptional level. Future studies should incorporate gene expression profiling, pathway analysis, and *in vitro* SGLT2 inhibition assays to validate this mechanism and determine whether direct inhibition or indirect modulation accounts for the observed reduction in SGLT2 expression.

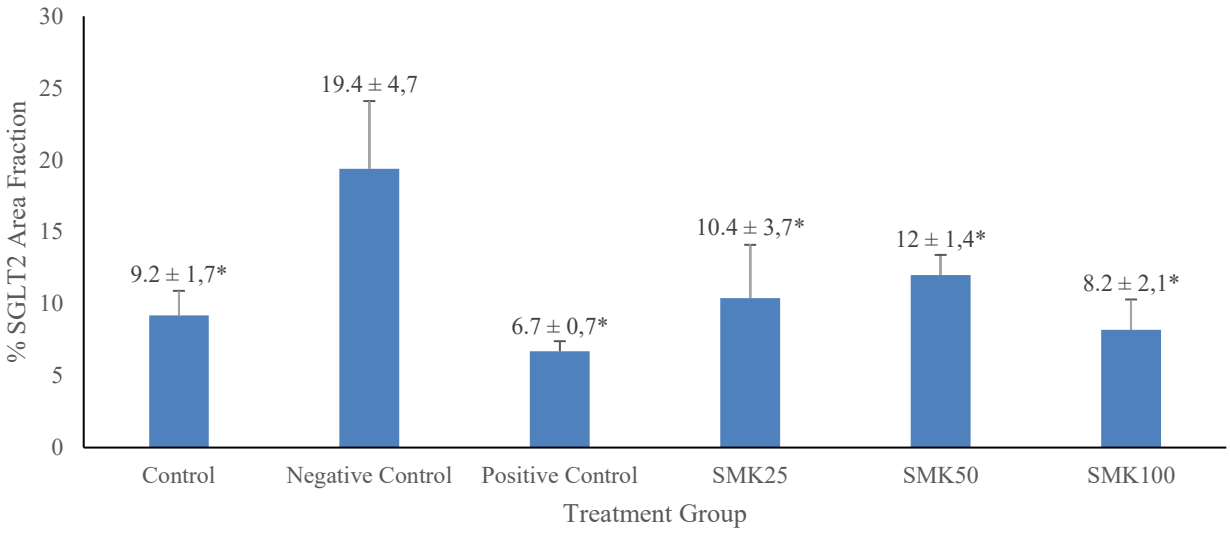

Figure 2 Percentage of SGLT2 expression area fraction in renal tubules across different groups. Values are expressed as mean ± SD (n = 4). * indicates a significant difference compared to the negative control group ($p < 0.05$, Post-hoc LSD).

Kidney histopathology

We evaluated tubular injury based on microscopic examination using PAS staining. As shown in **Figure 3**, the damage that occurred in each group is shown. Semiquantitative analysis was conducted by observing tubular injury parameters from 10 different fields of view in each test animal.

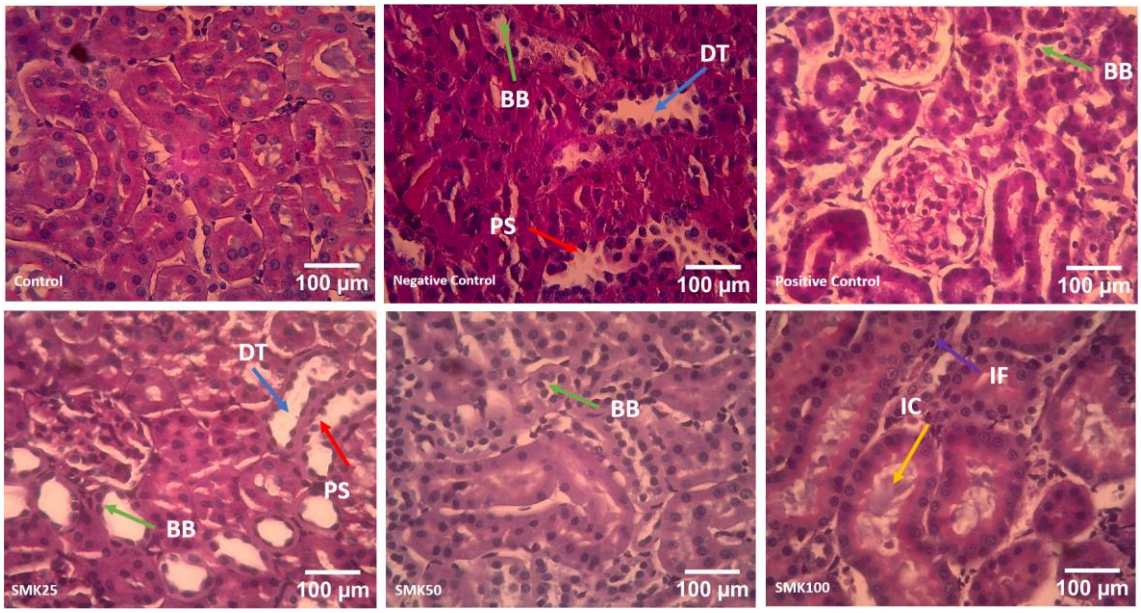

Figure 3 Microscopic appearance of the kidney (PAS staining, 640× magnification). Green arrow: loss of brush border; purple arrow; inflammation; yellow arrow; intraluminal cast; red arrow: epithelial cell thinning; blue arrow; tubule dilation. Tubular injury was more severe in the negative control group compared to the SMK-treated groups. Scale bar = 100 µm.

The average tubular injury scoring calculation of renal histopathology in the *Swietenia macrophylla* King treatment group, positive control group, and control group was lower than in the negative control group and significantly different statistically with a *p*-value = < 0.001 (**Figure 4**).

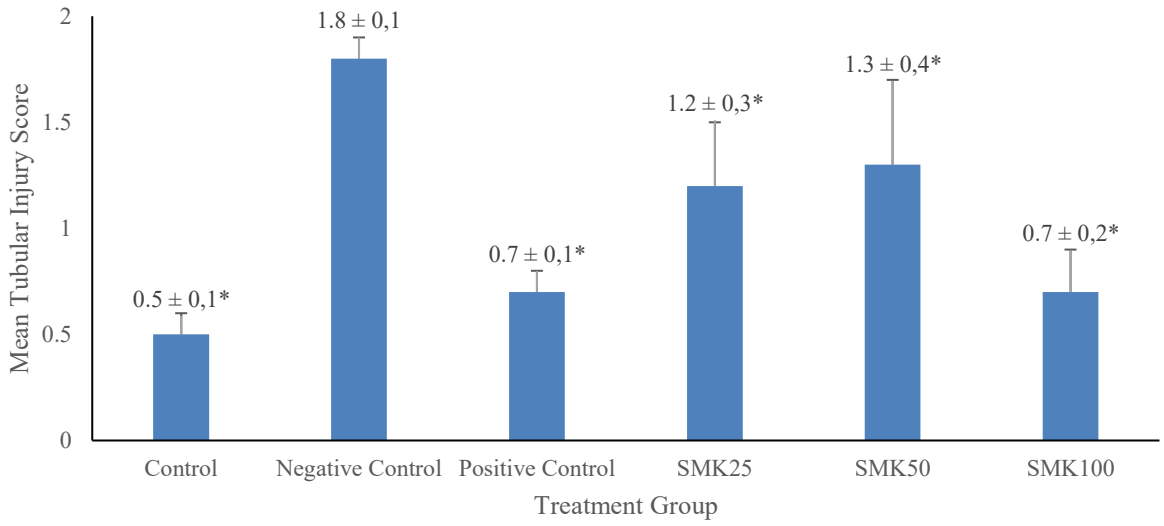

Figure 4 Average tubular injury score in each experimental group. Values are expressed as mean ± SD. * indicates a significant difference compared to the negative control group ($p < 0.05$, Post-hoc LSD).

Hyperglycemia leads to various microvascular complications, one of which is impaired kidney function that can progress to diabetic nephropathy [28]. The results of this study demonstrate an improvement in kidney damage, particularly in the tubular injury parameter, as evidenced by a significant decrease in injury scores in the groups treated with *Swietenia macrophylla* King extract across all 3 dose levels compared to the negative control group. This suggests that *Swietenia macrophylla* King extract has the potential to repair tubular injury.

Supporting evidence comes from a study by Basy *et al.* [22], which reported that the ethanol extract of *Swietenia macrophylla* King seeds significantly reduced serum creatinine, malondialdehyde (MDA), and urinary protein levels in streptozotocin-induced diabetic rats. These findings indicate that the extract may improve kidney function in hyperglycemic conditions. The therapeutic effects of *Swietenia macrophylla* King seed extract are partly attributed to its saponin content, which possesses antidiabetic properties. Saponins are believed to contribute to the management of diabetic nephropathy by modulating oxidative stress, reducing blood pressure and kidney hypertrophy, and downregulating the expression of TGF-β1 and fibronectin—key mediators involved in the progression of renal fibrosis and structural damage [29].

Conclusions

This study demonstrates that *Swietenia macrophylla* King extract effectively reduces blood and urinary glucose levels, downregulates the expression of sodium-glucose co-transporter 2 (SGLT2), and exerts renoprotective effects by attenuating tubular injury in diabetic conditions. This study is among the first to demonstrate that *Swietenia macrophylla* exerts antidiabetic and nephroprotective effects through SGLT2 modulation, highlighting a novel mechanism of action for this medicinal plant. These findings provide significant scientific value by identifying a natural compound with dual antidiabetic and renoprotective properties, potentially serving as an alternative or complementary strategy to conventional diabetes therapies.

However, this study has limitations. Being preclinical, the results may not fully represent the complexity of human diabetes. Additionally, although SGLT2 downregulation was demonstrated at the tissue level, the mechanistic link between SMK constituents and SGLT2 remains speculative. Future research should employ molecular docking, gene expression studies, and *in vitro* assays to confirm this mechanism, alongside clinical investigations to validate therapeutic efficacy. Additionally, the relatively small sample size (n = 4 per group) may reduce statistical power and limit the

generalizability of these findings; larger studies are needed to strengthen the evidence base.

Acknowledgements

The researchers would like to thank the Pharmacology and Therapy Department, laboratory staff, and all the colleagues who contributed to this research. This research was supported by the Community Fund Grant, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Indonesia.

Declaration of Generative AI in Scientific Writing

The authors acknowledge the use of generative AI tools (Grammarly) for language editing and grammar correction. No content generation or data interpretation was performed by AI. The authors take full responsibility for the content and conclusions of this work

CRediT author statement

FBA Ummiyah: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing-Original Draft. **Setyo Purwono**: Conceptualization, Supervision. **Eti Nurwening Sholikhah**: Conceptualization, Supervision, Funding acquisition, Writing-review & Editing.

References

[1] DGA Budiyasa, NK Noviantari and NKAT Hapsari. Diabetes support system in efforts to improve therapeutic adherence and blood glucose control in type 2 diabetes mellitus patients. *Waarmadewa Minesterium Medical Journal* 2024; **3(1)**, 28-32.

[2] International Diabetes Federation. Diabetes basic facts & figures, Available at: https://idf.org/about-diabetes/facts-figures/, accessed July 2026.

[3] NT Saputra, IN Suartha and AAGO Dharmayudha. Diabetogenic agent streptozotocin to make male white rats diabetes mellitus. *Buletin Veteriner Udayana* 2018; **10(2)**, 116.

[4] RH Unger and DW Foster. *Diabetes mellitus*. *In*: JD Wilson and DW Foster (Eds.). Williams Textbook of Endocrinology. WB Saunders, Philadelphia, 1992.

[5] P Auliya, F Oenzil and ZDD Rofinda. Overview of blood glucose levels in overweight and obese students of the faculty of medicine, Andalas University. *Jurnal Kesehatan Andalas* 2016; **5(3)**, 528-533.

[6] K Alipin, EP Sari, M Madihah, T Setiawati, N Ratningsih and DM Malini. Kidney histology in streptozotocin-induced diabetic male Wistar rats treated with combined extract of Temulawak Rhizome and Belimbing Wuluh fruit. *Nusantara Bioscience* 2017; **9(3)**, 312-317.

[7] H Osorio, R Bautista, A Rios, M Franco, A Arellano, H Vargas-Robles, E Romo and B Escalante. Effect of phlorizin on SGLT2 expression in the kidney of diabetic rats. *Journal of Nephrology* 2010; **23(5)**, 541-546.

[8] P Made and PS Dharma. Diabetes therapy with SGLT-2 inhibitors. *Cermin Dunia Kedokteran* 2019; **46(6)**, 452-456.

[9] Kurniawan and PI Suryajaya. Dapagliflozin: A new therapy for diabetes mellitus. *Continuing Professional Development* 2015; **42(11)**, 817-822.

[10] A Hendrajaya. Terapi penghambat sodium glucose co-transporters-2 (SGLT-2) dalam pengobatan diabetes melitus tipe-2 (DM-2): Tinjauan pustaka. *Intisari Sains Medis* 2021; **12(1)**, 131-136.

[11] D Cheta. Animal models of type I (insulin-dependent) diabetes mellitus. *Journal of Pediatric Endocrinology & Metabolism* 1998; **11(1)**, 11-19.

[12] Yulianta, NM Rina, KTP Gelgel and IM Kardena. Toxicity effect of red betel leaf extract on the microscopic picture of alloxan-induced diabetic white rat kidney. *Buletin Veteriner Udayana* 2013; **5(2)**, 114-121.

[13] AE Nugroho. Review: Animal models of diabetes mellitus: Pathology and mechanism of some diabetogenics. *Biodiversitas Journal of Biological Diversity* 2006; **7(4)**, 378-382.

[14] N Nursakinah, AD Djalil and W Utaminingrum. 2017, Antidiabetic effectiveness test of ethyl acetate fraction of *Swietenia macrophylla* king leaf (*Swietenia macrophylla* King) on glucose-induced male rats. Master Thesis. Universitas Muhammadiyah Purwokerto, Jawa Tengah, Indonesia.

[15] M Muthmainah, I Nurwati, S Handayani, B Saptiwi and S Marufah. *Swietenia macrophylla*

king (*Swietenia macrophylla* king) seed isolate improves histopathological features of hepar of type 2 DM model rats. *Smart Medical Journal* 2021; **4(2)**, 73-82.

[16] Directorate of Drug Safety. *Quality and import-export supervision, N. food and drug administration of the republic of Indonesia*. Directorate of Drug Safety, Indonesia, 2022.

[17] Z Shiming, KK Mak, MK Balijepalli, S Chakravarthi and MR Pichika. Swietenine potentiates the antihyperglycemic and antioxidant activity of Metformin in Streptozotocin induced diabetic rats. *Biomed Pharmacother*. 2021; **139**, 111576.

[18] R Kurnijasanti, G Wardani, MR Mustafa and SA Sudjarwo. Protective mechanism pathway of *Swietenia macrophylla* extract nanoparticles against cardiac cell damage in diabetic rats. *Pharmaceuticals* 2023; **16(7)**, 973.

[19] N Fratiwi, S Sarani, G Agastia and M Isrum. Aktivitas antiinflamasi ekstrak etanol daun kirinyuh (*Chromolaena odorata* L.) dan pengaruhnya terhadap kadar interleukin 6 (IL-6) pada tikus jantan galur wistar. *Jurnal Pharmacia Mandala Waluya* 2022; **1(2)**, 54-67.

[20] DJ Cada, TL Levien and DE Baker. Dapagliflozin. *Hospital pharmacy* 2014; **49(7)**, 647-662.

[21] S Bonner-Weir, DF Trent, CJ Zmachinski, ET Clore and GC Weir. Limited B cell regeneration in a B cell-deficient rat model: Studies with dexamethasone. *Metabolism* 1981; **30(9)**, 914-918.

[22] LL Basy, S Lestari and S Kadarsih. The effects of the ethanolic extract of *Swietenia macrophylla* King seeds (Swietenia macrophylla King) on the renal function of streptozotocin-induced diabetic rats. *Journal of the Medical Sciences* 2015; **47(2)**, 51-58.

[23] G Sahgal, S Ramanathan, S Sasidharan, MN Mordi, S Ismail and SM Mansor. Phytochemical and antimicrobial activity of Swietenia mahagoni crude methanolic seed extract. *Tropical Biomedicine* 2009; **26(3)**, 274-279.

[24] DW Sumekar and S Fauzia. The effectiveness of *Swietenia macrophylla* king seed (*Swietenia Mahagoni*) as a treatment of diabetes mellitus. *Medical Journal of Lampung University* 2016; **5**, 1-10.

[25] B Joseph and D Jini. Antidiabetic effects of *Momordica charantia* (bitter melon) and its medicinal potency. *Asian Pacific Journal of Tropical Disease* 2013; **3(2)**, 93-102.

[26] WA Saka, OS Oyekunle, TM Akhigbe, OO Oladipo, MB Ajayi, AT Adekola, AI Omole and RE Akhigbe. *Andrographis paniculata* improves glucose regulation by enhancing insulin sensitivity and upregulating GLUT 4 expression in Wistar rats. *Frontiers in Nutrition* 2024; **11**, 1416641.

[27] LV Vigneshwaran and KG Lalitha. *In silico* evaluation of antidiabetic molecules of the seeds of Swietenia mahagoni Jacq. *International Journal of Pharmaceutical and Phytopharmacological Research* 2017; **6(1)**, 41.

[28] B Kiberd. The chronic kidney disease epidemic: Stepping back and looking forward. *Journal of the American Society of Nephrology* 2006; **17(11)**, 2967-2973.

[29] H Tae-sun, C Ji-Young, P Hye-Young and L Jin-Seok. Gingseng total saponin improves podocyte hyperpermeability induced by high glucose and advanced glycosylation endproducts. *Journal of Korean Medical Science* 2011; **26(10)**, 1316-1321.