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Impact of Steviol Glycosides on Renal Functions Using Rats Models

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ABSTRACT

Introduction: *Stevia rebaudiana* is a natural sweetener with reported therapeutic properties. Although native to South America, it is now cultivated globally in tropical and subtropical regions. In Nigeria, the natural plant is rarely available; instead, commercially produced steviol glycosides are widely consumed. It is therefore important to evaluate whether these commercial products confer renal effects comparable to those reported for the natural plant.

Aim: The aim of this study was to determine the effects of steviol glycosides on renal indices.

Methods: Twenty Sprague Dawley rats weighing between 150g to 200g were randomly assigned into four groups (n = 5): control, 4 mg/kg body weight (BW), 8 mg/kg BW, and 12 mg/kg BW of commercial obtained steviol glycosides. Steviol glycosides was administered daily for 45 days, 24 hour urine samples were collected from each rat using metabolic cages prior to scarifying the rats for urine assay. After sacrifice, blood and kidney samples were obtained; renal biomarkers assessed included serum and urinary creatinine, urea, cystatin C, electrolytes, urinary protein, and kidney histology. Data were analyzed using one-way analysis of variance (ANOVA) with significance set at $P < 0.05$.

Results: No significant differences were observed in serum creatinine, electrolytes, or urinary protein. Serum urea was significantly reduced at 12 mg/kg, while cystatin C was lower at 4 mg/kg. Kidney histology was normal, with mild vasodilation in treated groups.

Conclusion: The reduction in urea concentrations and cystatin C observed in some groups in this study implies that the filtration function of the kidney is in good state. We therefore conclude that commercially packaged stevia glycosides did not adversely affect renal function or structure and may exhibit protective effects comparable to those of natural *Stevia rebaudiana*.

Keywords: *Stevia rebaudiana*; Steviol glycosides; Renal function; Cystatin C; Kidney histology

INTRODUCTION

In recent years, the use of artificial sweeteners has significantly increased, attracting attention from the food industry as potential food additives. Sweeteners are chemical compounds, either naturally occurring or synthetically produced, that possess a sweet taste, making them suitable as sugar substitutes. Most artificial sweeteners are not absorbed by the human body and can be classified based on their origin (natural or synthetic), texture (powder or syrup), and nutritional value (caloric or non-caloric) (European Food Safety Authority [EFSA], 2014). Stevia glycoside is a white to light yellow powder, odourless or having a slight characteristic odour. About 200 - 300 times sweeter than sucrose

Steviol glycosides consist of a mixture of compounds containing a steviol backbone conjugated to any number or combination of the principal sugar moieties (glucose, rhamnose, xylose,

fructose, arabinose, galactose and deoxyglucose) in any of the orientations occurring in the leaves of *Stevia rebaudiana* Bertoni. The product is obtained from the leaves of *Stevia rebaudiana* Bertoni. The leaves are extracted with hot water and the aqueous extract is passed through an adsorption resin to trap and concentrate the component steviol glycosides. The resin is washed with a solvent alcohol to release the glycosides and the product is recrystallized from methanol or aqueous ethanol. Ion exchange resins may be used in the purification process. The final product may be spray-dried (Momtazi-Borojeni *et al.*, 2017).

Steviol glycosides do not induce a glycemic response when ingested, because humans cannot metabolize stevia, (Geuns *et al.*, 2006). The acceptable daily intake (ADI) for steviol glycosides, expressed as steviol equivalents, has been established to be 4 mg/kg

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body weight/day, and is based on no observed adverse effects of a 100 fold higher dose in a rat study (EFSA, 2010).

Many artificial sweeteners, such as cyclamates and saccharin, are high-calorie sugars and have been identified as potential carcinogens (Brahmachari *et al.*, 2011). Aspartame, in particular, has been associated with an increase in total cholesterol (TC), low-density lipoprotein (LDL), and triglycerides, while reducing high-density lipoprotein (HDL) (Eiya and Osunbor, 2023). Additionally, aspartame consumption in rats has been linked to increased plasma viscosity and fibrinogen concentration (Eiya and Osunbor, 2023). On the other hand, *Stevia rebaudiana* is a natural sweetener known for its various therapeutic properties, including antihypertensive, anti-obesity, and antihyperglycemic effects (Díaz, 2013).

Chronic kidney disease (CKD) is an increasing health concern, particularly in low and middle income countries such as those in sub Saharan Africa (Oluyombo *et al.*, 2013). The Global Burden of Disease (GBD) study ranked CKD as the 19th leading cause of death in 2013; recent studies have shown that due to hanging population dynamics and evolving risk accumulation mean that the global burden of kidney disease is increasing relentlessly to become the fifth most common non communicable disease (NCD) driver of mortality by 2040. Kidney disease increases the risk of mortality, morbidity and disability, decreases quality of life and has profound individual and health system level economic consequences, as well as dire environmental impacts. Kidney disease is under recognized and under resourced. Recognizing kidney disease as a major driver of NCD related mortality will translate into coordinated global efforts to minimize the burden of kidney disease and will save lives (Francis *et al.*, 2024).

Lifestyle factors such as diet, obesity, and physical inactivity contributes to renal impairment, several studies have established a strong and consistent relationship between oxidative stress, lipid peroxidation products, and nephrotoxicity (Yousef, *et al.*, 2018, Mamoulakis, 2019).

Artificial sweeteners have also been linked to an increased risk of type 2 diabetes mellitus (T2DM) (Renwick & Tarka, 2008). Diabetic kidney disease (DKD) is a major cause of kidney failure worldwide (Reidy *et al.*, 2014). People with diabetes are at a high risk of renal failure due to the effects of elevated glucose levels, which induce cellular changes affecting various kidney cell types, including endothelial cells, smooth muscle cells, mesangial cells, podocytes, tubular and collecting duct cells, inflammatory cells, and myofibroblasts (Vallon & Komers, 2011).

Cystatin C is an early glomerular marker and a cysteine protease inhibitor produced and released at a constant rate by all nucleated cells. Since it is freely filtered by the glomerulus, it has been proposed as a more accurate predictor of glomerular filtration rate (GFR) than serum creatinine, as it is not significantly influenced by race or muscle mass (Filler & Bokenkamp, 2005). Additionally, cystatin C has demonstrated strong clinical potential as a biomarker for acute kidney injury (AKI) (Murty *et al.*, 2013). However, creatinine and urea, along with electrolytes, remain the

most commonly used biomarkers for assessing kidney function (Tietz, 2008).

This study examines the effects of stevia glycoside on routinely used kidney biomarkers, including cystatin C as an early glomerular biomarker, as well as its impact on kidney morphology.

MATERIALS AND METHODS

Ethical Approval

Ethical approval was obtained from the Research Ethics Committee, College of Medical Sciences University of Benin, Benin City, Nigeria with approval number REC Approval No: CMS/REC/2026/925. This study was conducted and reported in accordance with the ARRIVE 2.0 guidelines for animal research to ensure methodological rigor, transparency, and reproducibility.

Experimental Design

This study utilized twenty (20) adult Sprague Dawley rats weighing between 150 g and 200 g were purchased from Ibadan, on arrival the rats were acclimatized for two weeks under standard environmental conditions, including a 12-hour light/dark cycle, adequate ventilation, and unrestricted access to standard rat chow and water *ad libitum*. The study adhered to the guidelines of the National Research Council (NRC, 2011), for the care and use of laboratory animals and the 3 R's in animal research Replacement, Reduction, and Refinement was adhered to in the determination of sample size. Commercially packaged stevia glycoside was bought from Hall mark supermarket on Sapele road, departmental store Benin City, Nigeria since the plants were not readily available. The various doses were now prepared based on the body weights of the rats.

Following the acclimatization period, the rats were randomly assigned into four groups (n=5 per group):

- Group 1 (Control): Received normal rat chow and distilled water.
- Group 2: Administered 4 mg/kg body weight (BW) of *Stevia rebaudiana* orally, daily.
- Group 3: Administered 8 mg/kg BW of *Stevia rebaudiana* orally, daily.
- Group 4: Administered 12 mg/kg BW of *Stevia rebaudiana* orally, daily.

Three doses of stevia glycoside were administered; the doses were determined based on the normal daily allowed intake of stevia which is 4 mg/kg bw (EFSA, 2010). Group 2 was administered 4 mg/kg bw of stevia, this was doubled in group 3 and tripled in group 4 while group 1 was the control. All doses were administered via oral gavage in a total volume of 5 ml per rat. Throughout the 45 day experimental period, all groups continued to have free access to standard rat chow and water.

At the end of the study, 24-hour urine samples were collected from the rats using metabolic cages. Following urine collection, the rats were then anesthetized using chloroform-soaked cotton wool in a box chamber and sacrificed upon loss of consciousness;

blood was then collected via cardiac puncture, and put into plain sample bottles. The kidneys were excised and fixed in formal saline for histological analysis.

Biochemical Analysis

Urine albumin levels were quantified using spectrophotometry, as described by Domon and Aebersold (2006). Serum cystatin C concentration was determined using the enzyme-linked immunosorbent assay (ELISA) method, as established by Engvall and Perlmann (1971). Electrolyte concentrations (Na^+ , K^+ , Cl^- , and HCO_3^-) in urine and serum were measured using the Ion Selective Electrode (ISE 4000). Serum urea levels were determined using the Blood Urea Nitrogen (BUN) test (Burtis and Ashwood, 1999). Serum and urinary creatinine levels were measured using the colorimetric method (Bonsnes and Tausky, 1945).

Histological assessment

Histology of the kidney was done according to the method of Bancroft and Gamble (2008). Slides were examined under a light microscope, and photomicrographs were captured for histological evaluation.

The kidney samples were collected from the rats, each rat was first anesthetized using chloroform vapor, and then a dissection procedure was performed to access the kidney. The kidneys were obtained from the dissected rat and fixed immediately in 10% Formol-saline prior to processing. They were later dehydrated by passing through varying and increasing concentration of alcohol, cleared in xylene and then the tissue was embedded in molten paraffin. The sections was stained with hematoxylin and eosin dye, and then mount the stained slides with DPX mountant, then covered with cover slip to avoid air bubbles. Sections were then examined under light microscope (Olympus Microscope) at a high

power magnification and photomicrographs were taken with a digital camera.

Statistical Analysis

All data obtained from the study were analyzed using GraphPad Prism software (version 8.1). Treated groups were compared to the control using Student's *t*-test. *P*-value of < 0.05 was considered statistically significant.

RESULTS

There was a significant reduction ($p < 0.05$) in serum urea concentrations in rats administered 12 mg/kg body weight stevia when compared to control, also there was a significant reduction ($p < 0.05$) in Cystatin C in the groups administered 4 mg/kg body weight and 8 mg/kg body weight stevia, however there was no significant difference ($p > 0.05$) in other groups when compared with control. Urine parameter showed a significant increase ($p < 0.05$) in urinary creatinine concentrations in the group administered 4.0 mg/kg body weight stevia when compared with control; other groups did not show any significant difference ($p > 0.05$) when compared with control see Table 1.

Histological findings

The histological analysis of this study showed a normal architecture of the tissue (kidney) when observed across the experimental groups compared with the control with an additional effect of vasodilatation and increase in blood flow which is described as active congestion. However the active congestion and vasodilatation appeared to be more intense with increase in dosage.

Table 1: Showing the mean values of Serum Urea, Creatinine, Cystatin C and electrolytes concentrations in Sprague dawley rats following Stevia administration.

Parameters	Control	4.0mg/kg	8.0mg/kg	12mg/kg
Serum urea (mg/dl)	49.00 $\pm$ 5.76	43.40 $\pm$ 2.46	40.60 $\pm$ 3.61	34.00 $\pm$ 3.11*
Serum creatinine (mg/dl)	0.475 $\pm$ 0.05	0.480 $\pm$ 0.02	0.4600 $\pm$ 0.03	0.4800 $\pm$ 0.02
Cystatin C	16.31 $\pm$ 0.45	12.76 $\pm$ 0.65*	11.36 $\pm$ 2.28*	16.51 $\pm$ 1.46
Serum sodium (mMol/L)	138.3 $\pm$ 0.85	138.8 $\pm$ 1.24	137.8 $\pm$ 1.02	140.6 $\pm$ 1.12
Serum potassium (mMol/L)	4.475 $\pm$ 0.32	4.220 $\pm$ 0.22	4.560 $\pm$ 0.13	4.280 $\pm$ 0.18
Serum bicarbonate (mMol/L)	20.25 $\pm$ 0.95	20.60 $\pm$ 1.36	23.20 $\pm$ 1.11	21.60 $\pm$ 0.81
Serum chloride (mMol/L)	106.3 $\pm$ 0.85	106.8 $\pm$ 1.16	106.4 $\pm$ 1.12	109.0 $\pm$ 1.00

* $P < 0.05$ indicates significant difference.

Table 2: Showing the mean values of urine electrolytes, urea concentration and creatinine concentration in Sprague dawley rats following Stevia administration

Parameters	Control	4.0mg/kg	8.0mg/kg	12mg/kg
Urine urea (mg/dl)	459.0 $\pm$ 37.70	481.6 $\pm$ 26.46	516.6 $\pm$ 49.62	556.2 $\pm$ 24.30
Urine creatinine (mg/dl)	7.770 $\pm$ 0.52	10.43 $\pm$ 0.72*	8.880 $\pm$ 0.99	9.122 $\pm$ 0.86
Urine protein (mg/dl)	50.63 $\pm$ 4.68	55.08 $\pm$ 6.07	60.22 $\pm$ 11.29	37.02 $\pm$ 3.89
Urine sodium (mMol/L)	43.10 $\pm$ 6.24	56.60 $\pm$ 1.86	57.00 $\pm$ 1.14	55.60 $\pm$ 2.21
Urine potassium (mMol/L)	36.85 $\pm$ 4.13	41.64 $\pm$ 1.21	38.76 $\pm$ 2.94	41.22 $\pm$ 2.19
Urine bicarbonate (mMol/L)	294.0 $\pm$ 3.51	216.8 $\pm$ 32.70	235.6 $\pm$ 34.49	278.8 $\pm$ 10.17
Urine chloride (mMol/L)	46.00 $\pm$ 4.30	47.00 $\pm$ 6.61	51.00 $\pm$ 3.15	47.80 $\pm$ 3.43

* $P < 0.05$ indicates significant difference.

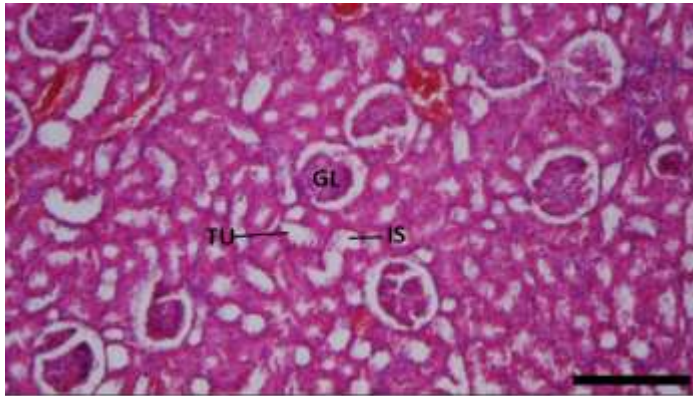


Plate 1: Control rat kidney showing normal renal architecture with intact tubules (TU), glomeruli (GL), and interstitial space (IS) (H&E; Scale bar: 100 μ m).

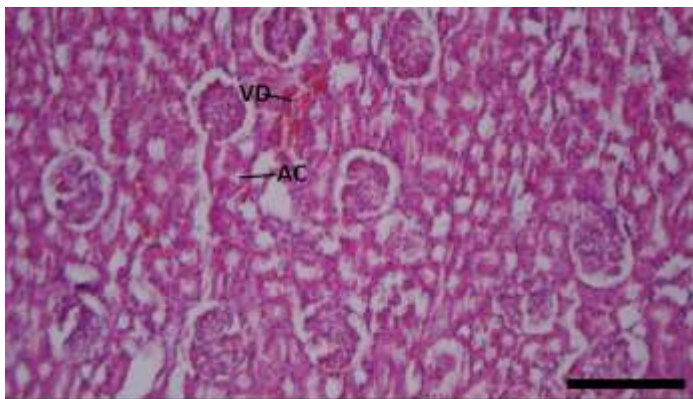


Plate 2: Photomicrograph of rat kidney following administration of 4 mg/kg body weight of stevia showing active interstitial congestion (AC) within the renal interstitium and vasodilatation (VD) of renal blood vessels (H&E; Scale bar: 100 μ m).

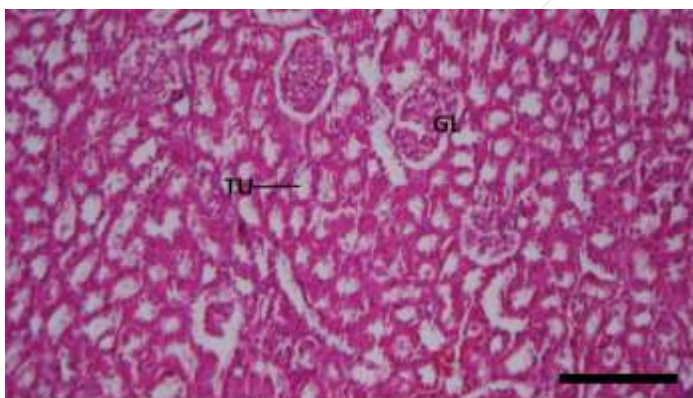


Plate 3: Photomicrograph of rat kidney administered 8 mg/kg body weight of stevia showing renal tubules (TU) and glomeruli (GL) with areas of active interstitial congestion (AC) (H&E; Scale bar: 100 μ m).

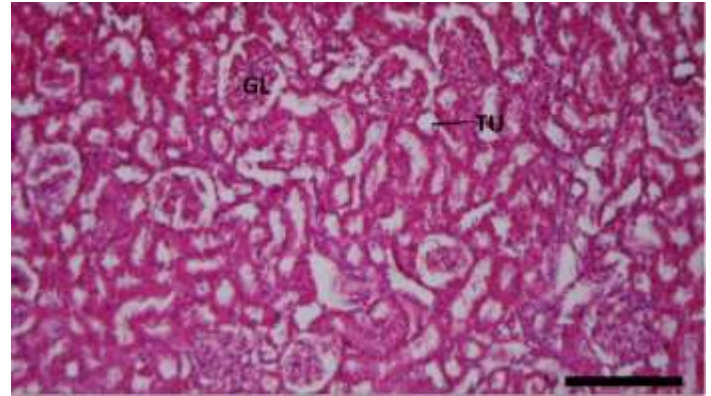


Plate 4: Photomicrograph of rat kidney administered 12 mg/kg body weight of stevia showing glomeruli (GL) and renal tubules (TU) with noticeable structural alterations in renal tissue architecture. (H&E; Scale bar: 100 μ m)

DISCUSSION

Stevia rebaudiana extract is a natural alternative to synthetic sweeteners, estimated to be 200 to 300 times sweeter than sugar (Elsaid *et al.*, 2019). This study aimed to evaluate the renal effects of commercially packaged stevia by analyzing key renal biomarkers and histological changes in rats.

The findings revealed a significant reduction in serum cystatin C concentrations in Group II (4 mg/kg BW), the reduction in cystatin c is an indication that the kidneys were not affected. Increase in cystatin C concentrations has been identified as an early and sensitive marker of glomerular filtration rate (GFR) (Filler & Bokenkamp, 2005; Murty *et al.*, 2013). This reduction suggests a potential enhancement in renal clearance or a renoprotective effect at lower doses. Although cystatin C levels in Group III (8 mg/kg) were also reduced, the change was not statistically significant, and values in Group IV returned to baseline, suggesting a dose-specific effect.

Serum creatinine levels remained unchanged across all groups, indicating stable renal function. Since creatinine levels typically rise only with significant renal impairment, the absence of elevation supports the non-nephrotoxic nature of steviol glycosides. These results are in line with Saarti and Althanoon (2024) who reported no changes in serum creatinine and urea. Elsaid *et al.*, (2019) reported decreased serum creatinine and enhanced creatinine clearance after stevia administration, while Azza *et al.* (2017) observed a 65% reduction in serum creatinine in diabetic rats treated with 38% stevia extract.

A significant decrease in serum urea was observed in Group IV (12 mg/kg), which may reflect enhanced protein metabolism or renal excretion. This observation is supported by Azza (2017), increased urinary urea and creatinine concentrations, particularly the significant rise in urinary creatinine in Group II, further reinforce improved renal excretory function.

Electrolyte levels (Na^+ , K^+ , Cl^- , and HCO_3^-) remained stable across all treatment groups. This suggests that tubular reabsorption and electrolyte handling were unaffected, further indicating the

preservation of nephron integrity. The consistency in electrolyte balance aligns with findings by Renwick and Tarka (2008), who reported that steviol glycosides do not disturb renal electrolyte dynamics.

Urinary protein levels were also unaffected, with the lowest proteinuria seen in the highest dose group (12 mg/kg). Since proteinuria is an early indicator of glomerular injury, the absence of elevated protein in urine supports stevia's renal safety profile. This observation correlates with Rizwan *et al.* (2018), who reported increased serum total protein and improved renal profiles in CKD patients treated with stevia.

Histological analysis revealed normal kidney architecture across all groups, with mild vasodilation and active interstitial congestion in the lower dose groups (4 and 8 mg/kg), but complete normalization at 12 mg/kg. These changes may represent physiological vascular adaptation rather than pathological injury. Previous studies have shown similar findings, where stevia induced systemic and renal vasodilation, diuresis, and natriuresis, particularly with prolonged use (Melis, 1992; Melis, 1996) reported that while short-term stevia use did not affect blood pressure, chronic administration (40–60 days) resulted in renal vasodilation, increased plasma flow, and stable GFR, which aligns with the vasodilatory changes seen in this study.

Overall, the study shows that commercially packaged stevia, at varying doses, does not impair renal function, and may even offer protective or modulatory effects on renal physiology, evidenced by favorable trends in cystatin C, urea, urinary excretion, and histopathology. These results are consistent with prior findings demonstrating the non-toxic and potentially beneficial renal effects of stevia (Geuns 2003; Goyal *et al.*, 2010; Ranjbar, 2020).

Conclusion: In conclusion, the study suggests that commercially packaged stevia is safe for renal function, as evidenced by stable serum creatinine, reduced serum urea and cystatin C levels, and preserved histological kidney structure. These outcomes affirm the potential nephroprotective role of stevia and support its viability as a natural sweetener without adverse renal effects, especially in populations with increasing reliance on alternative sweeteners.

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