

The Negative Effects of Using Some Artificial Sweeteners on Some Physiological Parameters in Albino Rats

Sara S. Rasheed^{1*}, Rawnaq Z. Fadhil², Noor H. Talib³, Salah M.M. Al-chalabi¹
Sara J. Kadhimi¹, Rawaa A. Khalaf¹

¹ Biotechnology Research Center, Al-Nahrain University, Baghdad, Iraq.

² Biology Department, Collage of Science, Al-Nahrain University, Baghdad, Iraq.

³ National Center for Hematology Research and Treatment, Al-Mustansiriyah University, 10053 Baghdad, Iraq

*Corresponding author email: sarah.s.r@nahrainuniv.edu.iq

ABSTRACT

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Background: Artificial sweeteners are widely consumed as sugar substitutes in various food products, as they are promoted for their low-calorie content, which helps manage blood sugar levels and aids in weight control. **Methodology:** This study examines the adverse effects of artificial sweeteners on specific physiological parameters in albino rats. We used twenty-five male albino rats weighing 180-250 g. The animals were divided into five groups (control, sucrose, stevia, stevia leaves, and saccharin), with five rats in each group. The duration of the experiment lasted 45 days, and the sweeteners were dissolved individually in water. **Results:** Rats showed a preference for water consumption with sucrose and saccharine, but consumed less with stevia leaves. The blood was collected for serum glucose, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), blood urea, serum creatinine, lipid profile, and C-reactive protein (CRP) measurement. Results showed a significant increase in glucose levels (mg/dL) at 176±17%, 119±10%, and 132±13%, respectively. Urea mg/dL(33±3%, 28±2 % and 31±1%) s. creatinine mg/dL(0.8±0.2%, 0.5±0.1% and 0.9±0.1%), GPT U/L (45±4%, 33±3 % and 41±3%) GOT U/L (128 ±11 %, 70±9 % and 129 ±12 %) cholesterol mg/dL(196 ±20 %, 162 ±12 % and 209 ±18 %) triglyceride mg/dL(178 ±17 %, 119 ±11 % and 187 ±16 %), HDL mg/dL(25 ±2 , 46 ±5 % and 36 ±3 %) and VLDL mg/dL(35 ±3 %, 23 ± 2 % and 22 ±1 %) of (sucrose, stevia and saccharin) groups when we compared them with the control group. It was found that dietary supplementation with stevia leaves didn't affect blood glucose 107 ±15 %, b.urea 24 ±5%, s.creatinine 0.4 ±0.04%, GOT 64±6 %, cholesterol 153 ±15 %, triglyceride 117 ± 2% , HDL 46±5 and VLDL 37±3 %. Except for GPT, there was a significantly elevated 33±3 % when we compared with the control group. Also, there were no significant changes in alkaline phosphatase levels in all five groups. As for CRP, there was no significant difference between the five groups; all groups were negative. **Conclusion:** It can be concluded that sweeteners must be used carefully because they have potential side effects due to their action on the Liver, kidneys, and lipid profile, as they cause significant changes in blood biochemical tests. It's vital to create high consciousness for consumers regarding its effects, especially for children

Keywords: Artificial sweeteners, stevia leaf, stevia, saccharin, lipid profile.

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INTRODUCTION

Sweeteners are substances that are used to add a sweet taste to food and drinks (1). They are classified into two

categories according to their source: natural and artificial (2). Natural sweeteners include sugars that occur naturally in fruits, honey, and milk, such as glucose, fructose, lactose, maltose, and sucrose, as well as sugar alcohols produced through the hydrogenation of sugars, including sorbitol, erythritol, and xylitol. Additionally, sweeteners derived from plants themselves, like stevia leaves, agave nectar, sugarcane extract, etc. (3,4,5, and 6). The second category of synthetic sweeteners is chemically manufactured to make sweetness without calories of sugar, such as aspartame, sucralose, saccharin, and extra (7). Artificial sweeteners are mainly used as alternatives to sugar for multiple reasons, like blood glucose level management, where patients with diabetes often use no-calorie or low-calorie sweeteners to control blood sugar level (8). Also, contribute to dental health by using toothpaste and sugar-free gum, as they prevent tooth decay. Also, they are used in weight control by reducing the calorie content of drinks and foods (9). Sugars impact several organs and have a serious risk factor, including kidney injury and liver damage; these effects can vary depending on individual health conditions, duration of consumption, and dosage (10). Several studies demonstrated that long-term sugar usage can elevate liver enzymes and induce oxidative stress, ultimately leading to liver damage (11). Another study showed that long-term consumption of sweeteners can cause liver hypertrophy (enlargement of liver cells) that leads to cellular changes and tumors (12). Similar to liver findings, high doses of these sweeteners can cause nephrotoxicity, alter the kidneys' filtration, and affect urine output (13). Artificial sweeteners can influence lipid metabolism, leading to elevated blood levels by altering the gut microbiota and affecting fat storage and metabolism (14). Numerous studies have shown that these sweeteners increase fat accumulation, particularly visceral and vascular fat, which can lead to heart disease. Additionally, excessive consumption of sweeteners can impair the body's ability to maintain energy balance, leading to weight gain (15). On the other hand, the evidence suggests that artificial sugar can increase insulin resistance and diabetes type2 which is linked to dyslipidemia and metabolic syndrome (16). Tumors take advantage of high glucose availability for their growth, as cancer cells have higher glucose metabolism than normal cells (17). Additionally, a high intake of sugar elevated insulin and insulin-like growth factor 1 in the blood; these hormones are associated with tumor growth and cancer cell proliferation (18). A diet with high sugar content means poor-nutrient foods like vegetables, fruits, and whole grains can increase the risk of cancer by preventing the body from essential nutrients that protect it against cancer (19). Continuous consumption of sugar over a long period can decrease blood cell (WBC) count, weaken immunity, resulting in chronic inflammation that is involved in cancer development. Chronic inflammation promotes tumor growth and metastasis (20). Furthermore, natural sweeteners (stevia leaves) have anti-inflammatory and anti-oxidant properties, not only protecting tissue but also reducing oxidative stress and preventing inflammation (21). This sweetener doesn't cause an insulin response, which can help control energy levels and reduce appetite, ultimately maintaining body weight (22). Several studies have shown that stevia extraction can help decrease cholesterol and triglyceride levels in blood, and support cardiac health through managing blood pressure (23). Stevioside and Rebuadioside are active components in stevia and have shown therapeutic influence on cancer cells, including antioxidant properties that neutralize free radicals and anti-inflammatory effects, which minimize inflammation in the body (24). A study by Iatridis, Nikos, *et al.* exhibits that stevia extraction induces apoptosis in tumor cells, and also prevents the proliferation in the same cancer cell line

METHODOLOGY

Animals: In this experiment, twenty-five mature Albino male rats, weighing between 250 and 180 grams, were used. Animals were housed in separate cages at the Biotechnology Research Center (BRC) of Al-Nahrain University, Iraq, and kept under controlled environmental conditions of temperature. $25 \pm 3^{\circ}\text{C}$, relative humidity 49 ± 5 and 12hr light /dark cycle.

This study commenced on November 1st and lasted for 45 days

The rats were divided equally into five groups; each group contains five rats, as shown below:

- Group I: control group received orally 1.5 mL of deionized water without any sweeteners.
- Group II: Rats received orally 40mg/kg of sucrose dissolved in 1.5 mL of deionized water.

- Group III: Rats received orally 1000mg/kg of commercial stevia dissolved in 1.5 mL deionized water.
- Group IV: Rats received orally 1000mg/kg from aqueous extract of stevia leaves mixed with 1.5 mL of deionized water.
- Group V: Rats received commercial orally saccharine 125mg/kg dissolved in 1.5 deionized water.

*All our doses of the sweeteners were given as acceptable daily intake(ADI) according to the European Food Safety Authority (EFSA)

Blood sampling:

At the end of the experiment, blood samples were collected under anaesthetized conditions, in clean centrifuge gel tubes, and allowed to clot for 10 minutes in a water bath at 37° C after that, they were centrifuged at 3000 r.p.m for 10 minutes to separate the serum, which was aspirated and transferred carefully into an Eppendorf tube and stored frozen until analysis. Serum was used to evaluate glucose level, urea, creatinine, GPT, GOT, lipid profile, and CRP.

*All tests were done by the Mindray BS-360E full automated biochemistry system, using the British Randox kit. The CRP test was measured manually by the Spinreact kit, Spain

RESULTS

Our results were evaluated using the One-Way ANOVA test; all results were expressed as mean $\pm$ SD, and values were considered significant at $P \leq 0.05$.

The results shown in Table (1) indicate a significant increase in glucose concentration at the $P \leq 0.05$ level in both the Sucrose and Saccharin groups. In contrast, the Stevia and Stevia leaf groups exhibited no significant increase compared to the control group.

Table (1): glucose level measurement (mg/dL)

Groups	Mean $\pm$	ST.DV%
Sucrose	176.1	17.1
Stevia	119.27	10.76
Stevia leaf	107.17	15.24
Saccharin	132.17	13.1
Control	112.3	18.8

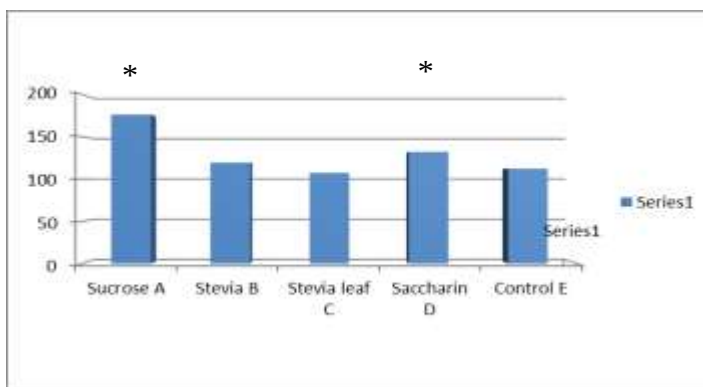


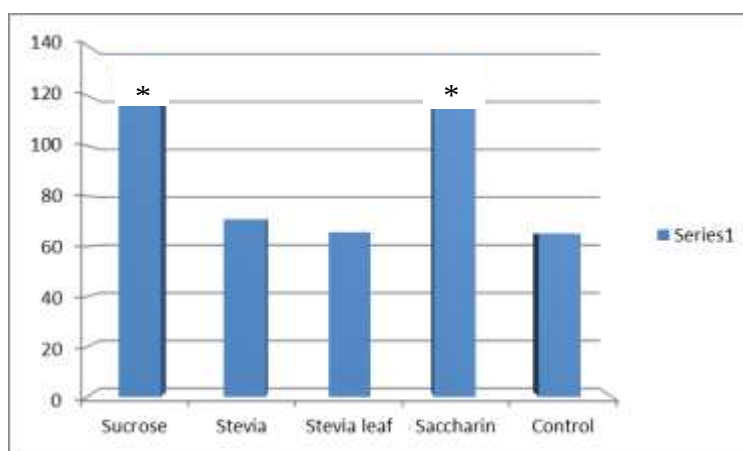
Figure (1): glucose level measurement (mg/dL)

* $P \text{ value} \leq 0.05$

Table (2) showed a significant increase in GOT levels at the $P < 0.05$ level in the Sucrose and Saccharin group. Regarding the stevia and stevia leaf groups, there was no significant increase compared to the control group.

Table(2): GOT level measurement (U/L)

Groups	Mean±	ST.DV%
Sucrose	128.67	11.5
Stevia	70.8	9.17
Stevia leaf	65.47	7.3
Saccharin	129.3	12.08
Control	64.9	6.36



Figure(2): GOT level measurement (U/L)

* P value ≤ 0.05

On the other hand, the results in Table (3) showed a significant increase in GPT levels concentration at the $P \leq 0.05$ level in all four groups compared with the control group.

Table (3): GPT level measurement (U/L)

Groups	Mean±	ST.DV%
Sucrose	45.8	4.42
Stevia	27.03	2.47
Stevia leaf	33.7	3.76
Saccharin	41.67	3.16
Control	22.3	1.77

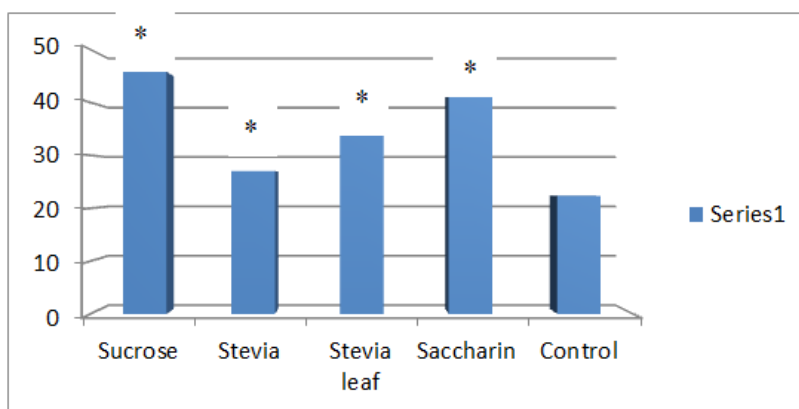


Figure (3): GPT level measurement (U/L)

* P value ≤ 0.05

The blood urea level in the sucrose and saccharin groups was significantly elevated at the $P \leq 0.05$ level, which is concerning. However, the means for stevia and stevia leaf did not differ significantly when compared with the control group, as shown in Table (4) below.

Table (4): Blood Urea level measurement (mg/dL)

Groups	Mean $\pm$	ST.DV%
Sucrose	33.6	3.26
Stevia	28.1	2.98
Stevia leaf	24.73	1.9
Saccharin	31.433	1.193
Control	24.43	5.29

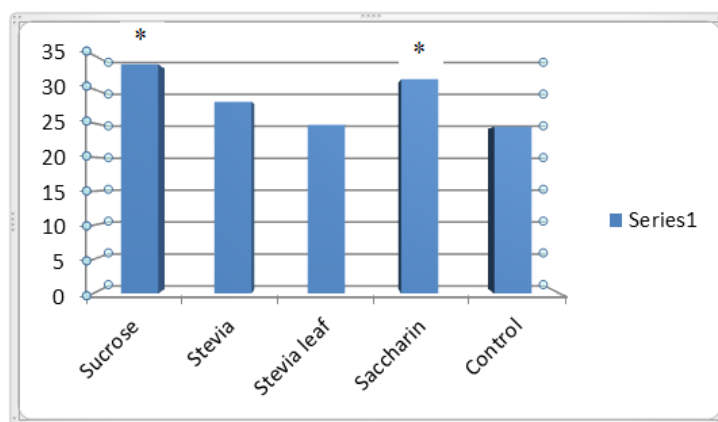


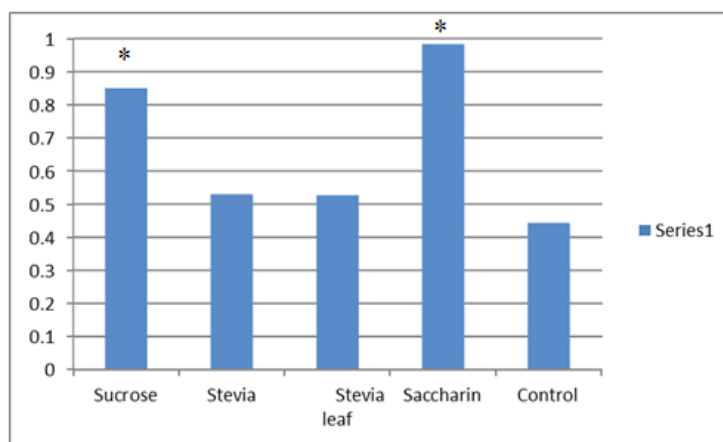
Figure (4) Blood Urea level measurement (mg/dL)

* P value ≤ 0.05

Table (5) showed a significant increase in the concentration of serum creatinine in groups 1 and 4 compared to the control. In contrast, its concentration remained within normal limits in the other groups, as shown below.

Table (5): Serum Creatinine level measurement (mg/dL)

groups	Mean±	ST.DV%
Sucrose	0.85	0.235
Stevia	0.53	0.1229
Stevia leaf	0.5267	0.0473
Saccharin	0.9833	0.115
Control	0.4433	0.0493



Figure(5): Serum Creatinine level measurement (mg/dL)

* P value ≤ 0.05

As for the lipid profile, cholesterol, triglycerides, and VLDL levels were significantly increased in the sucrose and saccharin groups, while there was no significant change in their concentration in the stevia and stevia leaves groups compared to our control group, as illustrated in the tables below.

Table (6): cholesterol level measurement (mg/dL)

Groups	Mean±	ST.DV%
Sucrose	190.8	20.7
Stevia	162.1	12.06
Stevia leaf	158.83	10.26
Saccharin	209.3	18.9
Control	153.13	15.61

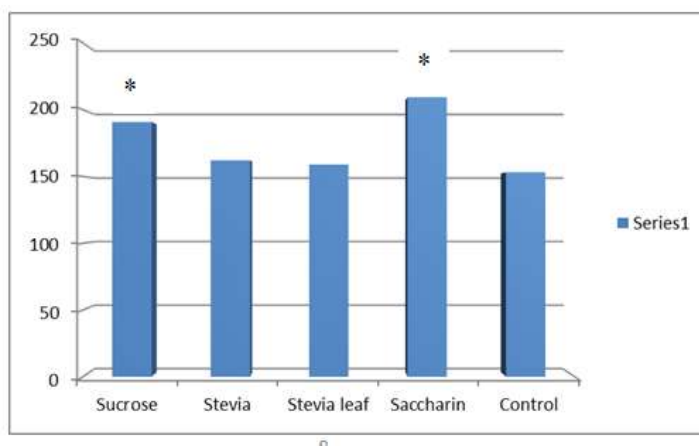


Figure (6): cholesterol level measurement (mg/dL)

* P value ≤ 0.05

Table (7): Triglyceride levels measurement (mg/dL)

Groups	Mean±	ST.DV%
Sucrose	178.1	17.7
Stevia	119.47	11.52
Stevia leaf	111.07	8.67
Saccharin	187.23	16.16
Control	110.5	12.72

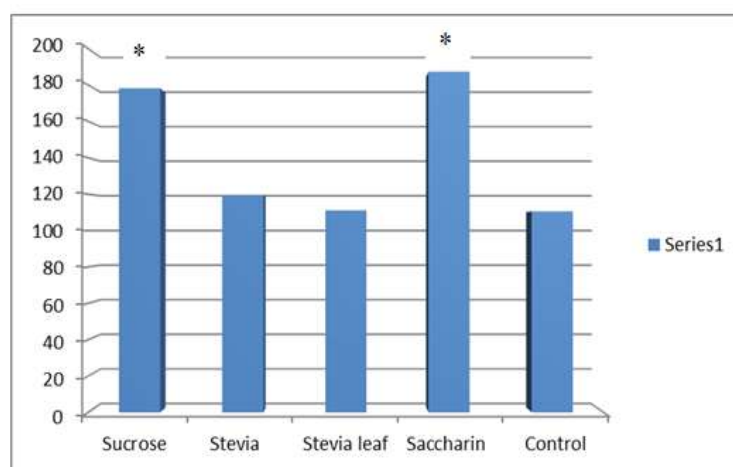


Figure (7): triglyceride level measurement (mg/dL)

* P value ≤ 0.05

Table (8): VLDL level measurement (mg/dL)

Groups	Mean	SD
Sucrose	35.63	3.55
Stevia	23.89	2.3
Stevia leaf	22.21	1.73
Saccharin	37.45	3.23
Control	22.1	2.54

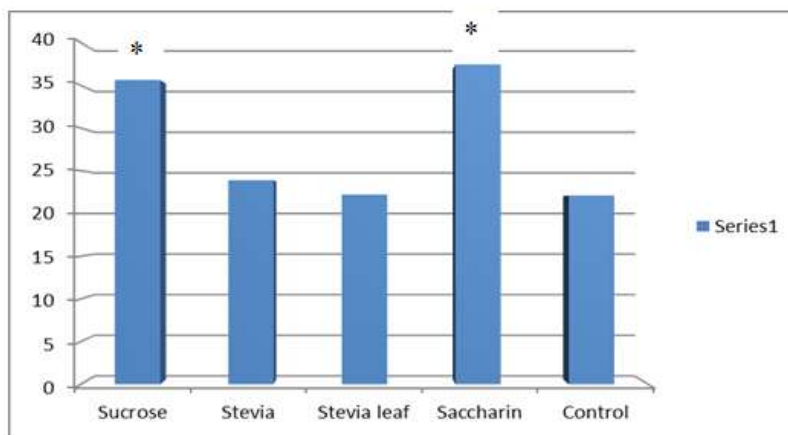


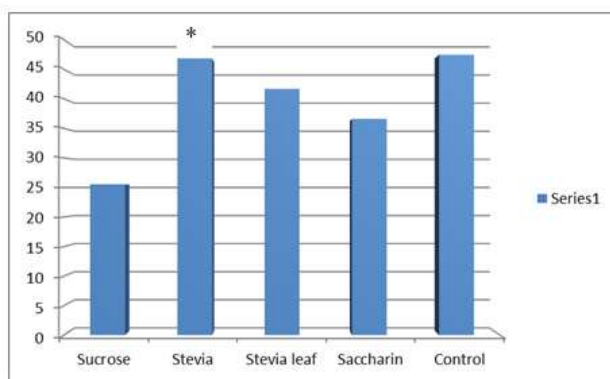
Figure (8) VLDL level measurement (mg/dL)

*** P value ≤ 0.05**

With regard to high-density lipoprotein (HDL) (the beneficial ones), the results showed a significant increase in the level of these fats in the stevia and stevia leaf groups compared to the control group. The concentration remains unchanged with no significant differences between the saccharin and sucrose groups when compared with the control group.

Table(9): HDL level measurement (mg/dL)

Groups	Mean±	ST.DV%
Sucrose	25.53	2.49
Stevia	46.83	5.25
Stevia leaf	41.7	3.03
Saccharin	36.6	3.58
Control	47.47	4.07



Figure(9): HDL level measurement (mg/dL)

* P value ≤ 0.05

DISCUSSION

Recently, the demand for general health has increased, and many people have chosen to use artificial sweeteners as a replacement for natural sugar to maintain their weight due to their low-calorie content and glycemic control, despite these sweeteners showing many adverse effects on the population (25). Multiple studies have demonstrated that an acceptable daily dose of artificial sweeteners, such as stevia, stevia leaves, and saccharin, has no significant influence on blood glucose levels (26, 27, and 28). In the current study, we investigated blood glucose levels in all five groups. Our results showed that there were no significant increases in blood glucose in groups (III, IV, and V) as they had zero-calorie sweeteners and then reduced serum glucose levels (29). However, the increase was only observed in the group of rats that received the sucrose solution (group II). In this study, we found an elevation in GPT and GOT levels in the group fed sucrose, likely due to liver cell injury, as indicated by the data from the rats fed sucrose (30). Sucrose contributes to ectopic lipid accumulation and is associated with non-alcoholic fatty liver disease (NAFLD), which can lead to increased liver enzymes (31). Saccharin and stevia, according to a study (32), led to oxidative stress and the accumulation of NO, which in turn reduced SOD levels and elevated liver enzymes. Stevioside and steviol glycoside are the main sweet parts and most important active components in stevia leaves (33). The hydrolyzed of stevia leaves occur in intestines to converts from steviol glycoside in to steviol and then transport to hepatocyte, in liver it conducted with sulfate or glucuronic acid resulting steviol sulfate and steviol glucuronide, this ingredient are water demands for excretion the excessive amount of this active component lead to excessive metabolism in liver, which may explain the elevation of GPT in stevia leaves group (34 and 35). The results found an elevation in the lipid profile in both stevia and saccharin. The assumed mechanism for this elevation is attributed to the role of artificial sweeteners in increasing food consumption by influencing intestinal epithelial taste receptors, which subsequently affects weight. Artificial sweeteners elevated oxidative stress levels and reduced NO production, which in turn reduced SOD, all of which contributed to an elevation in LDL, cholesterol, and free fatty acids (32). On the other hand, the elevation of lipid profile in natural sweeteners (sucrose) is attributed to the mechanism that sucrose consumption raises the level of Acetyl Co-A, the source for fatty acid synthesis from glucose, which in turn increases lipid storage in the liver and subsequently causes obesity and glucose intolerance (31). Renal function results revealed an elevation in urea and serum creatinine, indicating kidney dysfunction. A study by Nabi *et al.* 2024 explained the effect of saccharine on the kidney, as this compound is not absorbed in the GIT and eliminated by the kidney. In this way, it causes injury by elevating oxidative stress and disrupting antioxidant enzymes, subsequently leading to tubule congestion and ultimately resulting in a defect in glomerular infiltration, which in turn elevates urea and creatinine levels in the blood (36).

CONCLUSION

It can be concluded that sweeteners must be used carefully because they have potential side effects due to their action on the Liver, kidneys, and lipid profile, as they cause significant changes in blood biochemical tests. It's vital to create high consciousness for consumers regarding its effects, especially for children.

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