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Biochemical Effects of Stevia Leaf Extract and Its Purified Glycosides in Animal Models: Implications and Considerations for the Food Industry

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ABSTRACT

This study aimed to compare the effects of some sweeteners obtained from Stevia rebaudiana Bertoni on some biochemical parameters in healthy rats. The sweeteners were a crude aqueous leaf extract, purified stevioside glycosides, and a commercial product of stevia. This information will be useful for the selection of ingredients for the food industry. Thirty adult male Albino rats were used for this study and were divided into five groups (n=6): a control group (T1) and the following treatment groups (T2) crude extract at a dose of 10 mg/kg (1:100, leaf powder: water), (T3) purified stevioside crystals, (T4) commercial stevia crystals, and (T5) sucrose. There were no significant differences between the groups in terms of final body weight and liver enzymes (ALT, AST). Blood glucose levels were most significantly reduced in the group given purified stevioside (T3). There were, however, some significant differences in renal parameters (urea and creatinine) between all groups. In particular, the sucrose-fed group (T5) exhibited the highest levels of urea and creatinine, while those of the crude extract group (T2) were the lowest. The levels of serum triglycerides (41.78 mg/dL) and cholesterol (92.33 mg/dL) were higher in the sucrose-fed group (T5) than in the stevia-treated groups, where they were lower. These results demonstrate the fact that different stevia treatments brought about different physiological effects and that purified steviol glycosides might have metabolic benefits over sucrose. This could, therefore, offer a scientific foundation for the use of stevia-based sweeteners in the development of functional foods and beverages for glycemia and metabolism control.

1-Introduction

The sudden rise of metabolic syndromes on a global scale has led to an increased demand in the food industry for safe, low-calorie sugar substitutes [1]. This, in turn, has put natural non-nutritive sweeteners under the spotlight in the race to achieve consumer palatability with fewer calories and less sugar, a goal set by public health programs and consumers seeking "clean-label" products [2].

It is a shrub that grows every year from South America, and it is famous for the sweet leaves. Sweeteners are the leaves of Stevia, and they are about 200–300 times sweeter than sucrose [3]. Steviol glycosides were recently allowed in foods since highly pure ones (≥95%) were approved by major food safety authorities like JECFA and the U.S. FDA [4].

This dichotomy, therefore, poses a major scientific and industrial challenge. Do the health-related biochemical effects of the whole extract- with its complex phytochemical matrix (flavonoids, phenolic acids, and other minor glycosides)- substantively differ from those of its isolated, purified glycosides? However, a fast-growing market segment that practices traditional use supports whole leaf or crude aqueous extracts of stevia, perceived as a more "natural" and less-processed ingredient [5,6]. This, therefore, poses a major scientific and industrial challenge: do the health-related biochemical effects of the whole extract- with its complex phytochemical matrix (flavonoids, phenolic acids, and other minor glycosides)- substantively differ from those of its isolated, purified glycosides [7].

The present evidence base is, therefore, very fragmented. While purified SGs are well known to have antihyperglycemic and antihypertensive properties in animal models [8,9], studies on crude extracts yield different results, perhaps influenced by the methods of extraction, phytochemical composition, and nonsweetening compounds [10]. Most importantly, however, the safety and efficacy assessments that usually inform regulatory approvals pertain to purified compounds [11,12]. The comparative metabolic impact of different stevia formulations-crude extract vs. purified glycosides vs. commercial blends-has not been explored in a head-to-head experimental setting that would be necessary for evidence-based decisions in food product development on such key biochemical endpoints as glycemic response, lipid metabolism, and markers of hepatic and renal safety [13,14].

Therefore, this study was designed to compare healthy rodent models on the effects of a defined crude aqueous stevia leaf extract, laboratory-purified stevioside, a product available commercially, and a control of sucrose on a broad panel of biochemical parameters. We hypothesize that the purified steviol glycosides will be more targeted and potent in their effects on glycemic control; therefore, the crude extract may present a different biochemical profile due to its composite nature. Thus, results from this study would contribute to filling an important knowledge gap, providing data that can be used by the food industry to select the best ingredients for their products, provide marketing claims related to health, and develop next-generation functional foods based on science.

2-Materials and Methods

2.1. Plant Material and Extract Preparation

Fresh leaves of *Stevia rebaudiana Bertoni* were harvested from the Medicinal Plants Unit, College of Agricultural Engineering Sciences, University of Baghdad, Iraq, in the autumn season of 2023. They were cleansed immediately after harvesting. Then, the leaves were dried in the shade at 25±2 °C until constant weight. A laboratory grinder crushed the dried leaves into a fine powder. The powder was stored in polyethylene containers at room temperature, shielded from light until used.

The crude aqueous extract (CAE) was prepared as follows with some modifications. One hundred parts by weight of leaf powder was taken, to which 1000 parts by weight of distilled water were added [15]. The suspension was

stirred at 60°C for 60 minutes with a magnetic stirrer. It was first filtered through muslin cloth to remove large particles, then through Whatman No. 4 filter paper, and lastly through 0.22 µm sterile membrane filter (Millipore). The clear filtrate, which is CAE, was stored at 4°C for a maximum period of 48 hours before stability indicating animal administration.

2.2. Purification of Steviol Glycosides

To obtain PSG from the CAE, a targeted purification process was used with food-grade ion-exchange resins, which would be relevant to the industry downstream. The CAE was passed through a chromatographic column of 3 cm × 60 cm packed sequentially with a cationic (LXS861) and an anionic (LXS865) adsorption resin (Sun Resin, China) as recommended by the manufacturer. This step will selectively isolate steviol glycosides from impurities such as pigments and phenolic compounds. The eluent was concentrated to dryness, and the PSG was crystallized.

Purity and primary glycoside profile of the white crystals obtained were confirmed by HPLC with standard references (stevioside and rebaudioside A, Sigma-Aldrich). The HPLC analysis indicated total steviol glycoside purity of 96.8%, with a ratio of stevioside to rebaudioside A of approximately 2.5:1 (Supplementary Figure S1). This purity level meets JECFA and FDA specs for high-purity steviol glycosides (≥95%).

2.3. Description of Commercial Stevia Product

The stevia sweetener used was "SteviaSweet Pure" (Brand X, SweetLeaf Co., USA). This was a commercial product, which was purchased from the local market in Baghdad, Iraq. The manufacturer claimed that his product contains 99% rebaudioside A as the major steviol glycoside and no bulking agent of any kind, erythritol, maltodextrin, or dextrose. Its label claimed purity of ≥95% steviol glycosides, which falls within the purity standards prescribed by the regulators for high purity stevia.

2.4. Experimental Design and Animal Husbandry

Obtain thirty (30) healthy adult male Albino rats weighing 150-200 g. House them in polypropylene cages under conditions of 12 h light/dark cycle at 22±2 °C with 55±10% humidity. Provide standard rodent diet and water ad libitum. The rats were acclimatized for one week and then were randomly assigned to five experimental groups of 6 rats in each by using a completely randomized design (CRD):

- Group T1 (Control): Was given no treatment only distilled water.
- Group T2 (PSG): Was given purified steviol glycosides orally.
- Group T3 (CAE): Was given the crude aqueous extract orally.
- Group T4 (Commercial): Was given a commercially available stevia sweetener powder orally.
- Group T5 (Sucrose): Orally administered a sucrose solution.

Dose Justification: The dose of 10 mg/kg body weight/day was chosen based on previous studies [6,7] and is equal to an estimated HED of around 1.6 mg/kg/day for humans using the standard conversion factor for rats (0.162). These values are in the ADI for steviol glycosides as set by JECFA (0-4 mg/kg body weight) and the FDA (GRAS). The experimental feeding period was continued for 28 consecutive days. Monitoring of body weight and general health was done on a weekly basis.

Blinding and randomization: The rats were randomly assigned to treatment groups through a computer-generated random number sequence. The investigators, responsible for dosing the animals, collecting samples, and performing the biochemical analyses, were blind to the treatment allocation until after all the data were finalized and statistically analyzed.

2.5. Sample Collection and Biochemical Analysis

At the end of the 28-day treatment, the animals were fasted for 12 hours, then they were anesthetized and euthanized by cardiac puncture. Blood samples were taken directly into sterile tubes, allowed to clot, and then centrifuged at 3000 × g for 15 min at 4°C to obtain serum; serum aliquots were stored at -18°C until analysis.

All metabolic and safety biomarkers were assayed in duplicate with kits from commercial enzymatic assays (Bio Research, Iraq) on a spectrophotometer. All procedures were carried out according to the instructions provided by the manufacturers; each sample was run in duplicate.

- Glycemic control was assessed by measuring fasting blood glucose at baseline and endpoint. The glucometer used for this purpose was validated with Accu-Chek.
- Lipid Profile: Serum levels of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were measured by enzymatic methods. Very-low-density lipoprotein cholesterol (VLDL-C) and low-density lipoprotein cholesterol (LDL-C) were calculated [10].
- Hepatic and Renal Function: Serum activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) reflect liver integrity. Urea and creatinine levels provided the other indices for renal function.

2.6. Statistical Analysis

All data are presented as mean ± standard deviation (SD). Statistical analysis was performed using the Statistical Analysis System (SAS Institute, version 9.4). One-way analysis of variance (ANOVA) was applied to determine significant differences among treatment groups for all parameters measured at the end of the study. Where ANOVA indicated significance ($p < 0.05$), Duncan's Multiple Range Test was used for post-hoc mean separation. A p-value of less than 0.05 was considered statistically significant.

3-Results

3.1. Body Weight Dynamics

The impact of the different treatments on the final body weight of the experimental animals is as shown in Figure 1. No significant changes in body weight were observed between any of the treatment groups and the control (T1) over the 28 days. One-way ANOVA indicated no significant effect of treatment on final body weight ($F(4, 25) = 0.89$, $p = 0.482$). The control group went through a slight non-significant decrease from an initial 200.67 g to 193.97 g. Similar minor changes were observed in the groups that received purified steviol glycosides (PSG, T2: from 188.00 g to 188.83 g), crude aqueous extract (CAE, T3: from 187.67 g to 181.33 g), and sucrose (T5: from 183.33 g to 181.50 g). The group given commercial stevia (T4) had a modest increase from 177.00 g to 184.00 g.

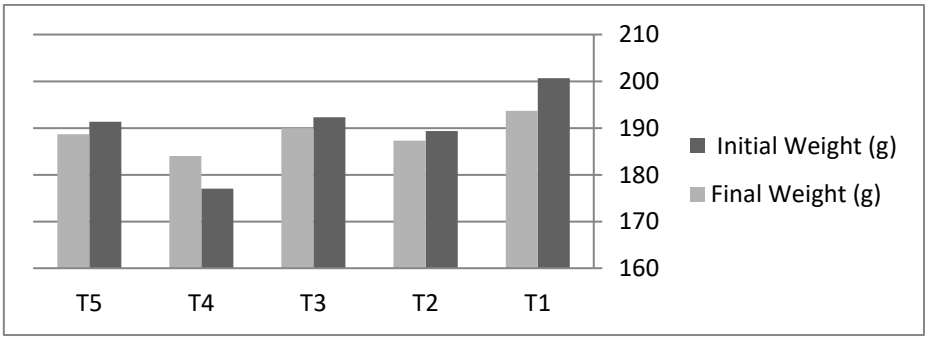

Figure 1. Effect of the studied treatments on rat body weight after the one-week acclimatisation period and at the end of the 28-day experimental period Bars represent mean body weight (g) ± SD (n=6 per group) No significant differences were detected among groups ($p > 0.05$).

3.2. Glycemic Response

The effects on fasting blood glucose (FBG) levels are presented in Figure 2. After 28 days, a significant reduction in FBG was observed exclusively in the group receiving purified steviol glycosides (PSG, T2: 79.33 mg/dL) compared to the sucrose (T5: 110.33 mg/dL), commercial stevia (T4: 113.67 mg/dL), and crude extract (CAE, T3: 127.67 mg/dL) groups. One-way ANOVA showed a significant main effect of treatment on final FBG ($F(4, 25) = 8.42$, $p < 0.001$). Post-hoc analysis (Duncan's test) confirmed that T2 was significantly different from T3, T4, and T5 ($p < 0.05$) but not from the control (T1: 96.67 mg/dL, $p = 0.183$). The sucrose group (T5) exhibited the highest endpoint FBG.

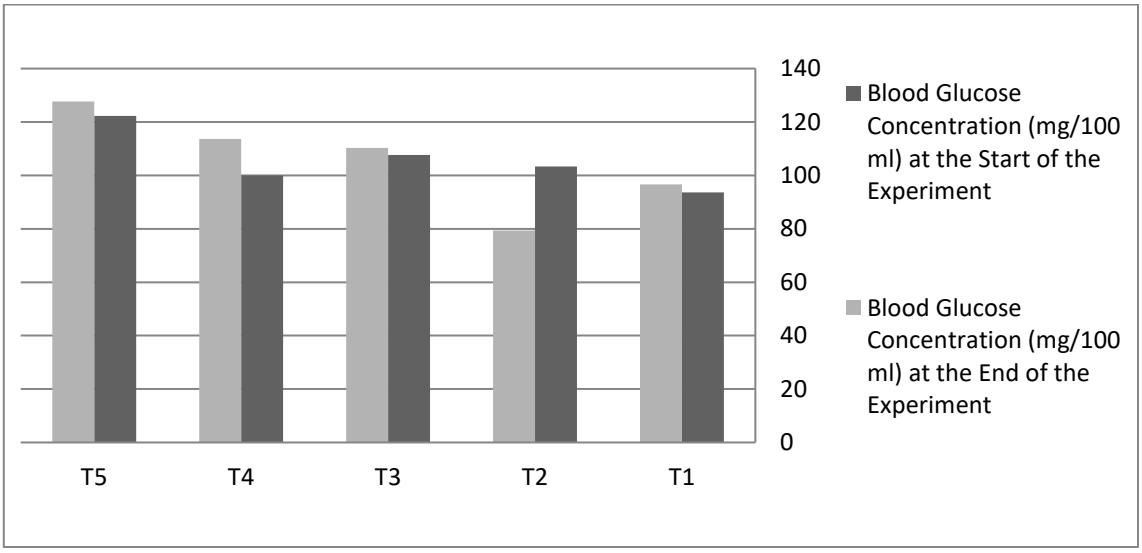

Figure 2. Effect of the treatments on blood glucose levels in rats after the one-week acclimatization period and at the end of the experimental period. The mean fasting blood glucose (mg/dL) ± SD (n=6 per group) is represented by bars. Different letters above bars indicate significant differences at $p < 0.05$ (Duncan's test). Glucose levels in T2 (PSG) were significantly lower, compared to T3, T4, and T5.

3.3. Hepatic Safety Biomarkers

Markers of hepatic function are shown in Figure 3. For ALT, ANOVA revealed a significant effect of treatment ($F(4, 25) = 5.67$, $p = 0.002$). The sucrose group (T5) displayed a significantly higher ALT (35.03 IU/L) compared to the control (T1: 26.17 IU/L) ($p = 0.008$). For AST, ANOVA also showed a significant effect ($F(4, 25) = 4.92$, $p = 0.004$). The PSG group (T2) showed a significantly lower AST (52.83 IU/L) compared to the control (T1: 71.33 IU/L) ($p = 0.011$). All stevia-treated groups (T2, T3, T4) had ALT and AST values within the established normal physiological ranges for healthy rats.

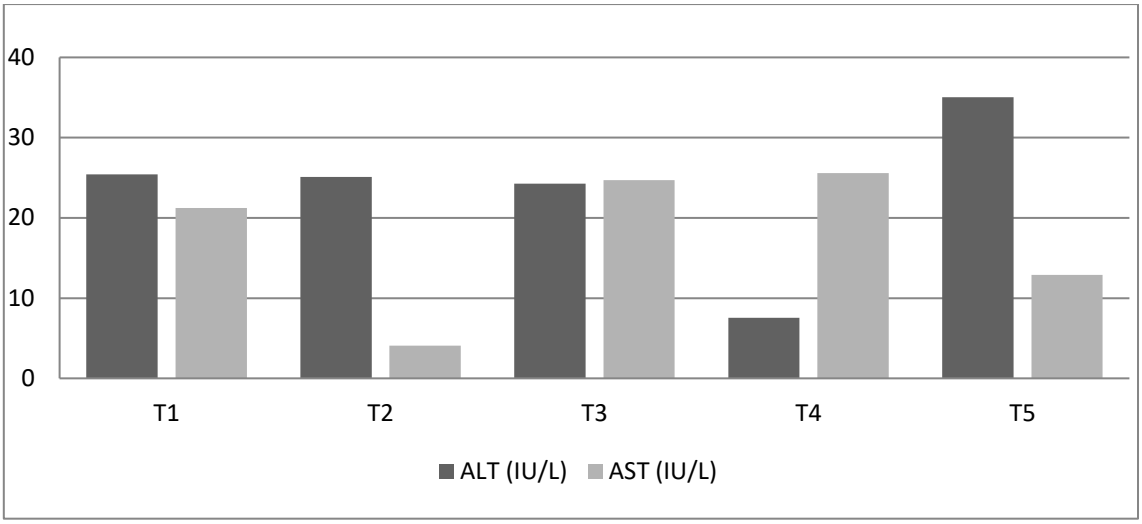

Figure 3. Effect of the studied treatments on liver enzyme concentrations in rats. Bars represent mean ALT and AST (IU/L) ± SD (n=6 per group). Different letters above bars indicate significant differences at $p < 0.05$ (Duncan's test).

3.4. Renal Function Biomarkers

Renal function parameters are presented in Figure 4. For urea, ANOVA showed a significant effect of treatment ($F(4, 25) = 3.87$, $p = 0.014$). The CAE group (T3) had the lowest urea level (28.00 mg/dL), which was significantly different from T4 (34.17 mg/dL) and T5 (33.83 mg/dL) ($p < 0.05$). For creatinine, ANOVA also showed a significant effect ($F(4, 25) = 4.21$, $p = 0.009$). Slight elevations in creatinine were noted in T3 (0.78 mg/dL), T4 (0.83 mg/dL), and T5 (0.82 mg/dL) compared to the control (T1: 0.61 mg/dL). All values remained within normal physiological limits for rats.

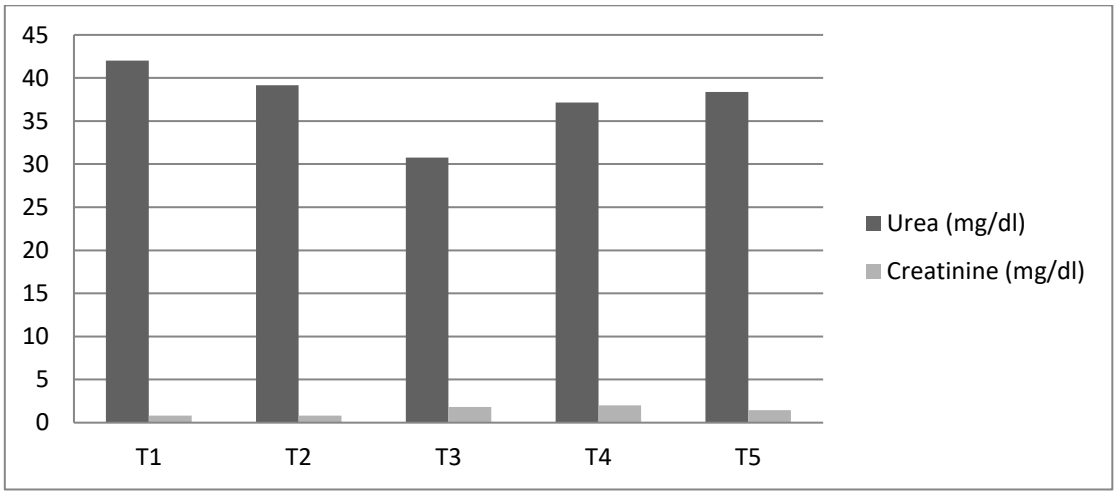

Figure 4. Effect of the studied treatments on urea and creatinine levels in rats. Bars represent mean urea (mg/dL) and creatinine (mg/dL) ± SD (n=6 per group). Different letters above bars indicate significant differences at $p < 0.05$ (Duncan's test).

3.5. Lipid Profile Modulation

The comprehensive lipid profile results are summarized in Figure 5. For triglycerides (TG), ANOVA showed a significant effect ($F(4, 25) = 7.23$, $p < 0.001$). The sucrose group (T5) exhibited significantly elevated TG (41.78 mg/dL) compared to all other groups ($p < 0.01$). For total cholesterol (TC), ANOVA showed a significant effect ($F(4, 25) = 6.45$, $p < 0.001$). T5 also showed significantly higher TC (92.33 mg/dL) compared to T1, T2, and T3 ($p < 0.05$).

For LDL-C, ANOVA showed a significant effect ($F(4, 25) = 5.12$, $p = 0.003$). T4 (23.98 mg/dL) and T5 (28.10 mg/dL) had significantly higher LDL-C compared to the control (T1: 15.19 mg/dL) ($p < 0.05$). For HDL-C, no significant differences were detected among groups ($F(4, 25) = 1.34$, $p = 0.282$). For VLDL, ANOVA showed a significant effect ($F(4, 25) = 6.89$, $p < 0.001$), with T5 showing the highest level (8.36 mg/dL).

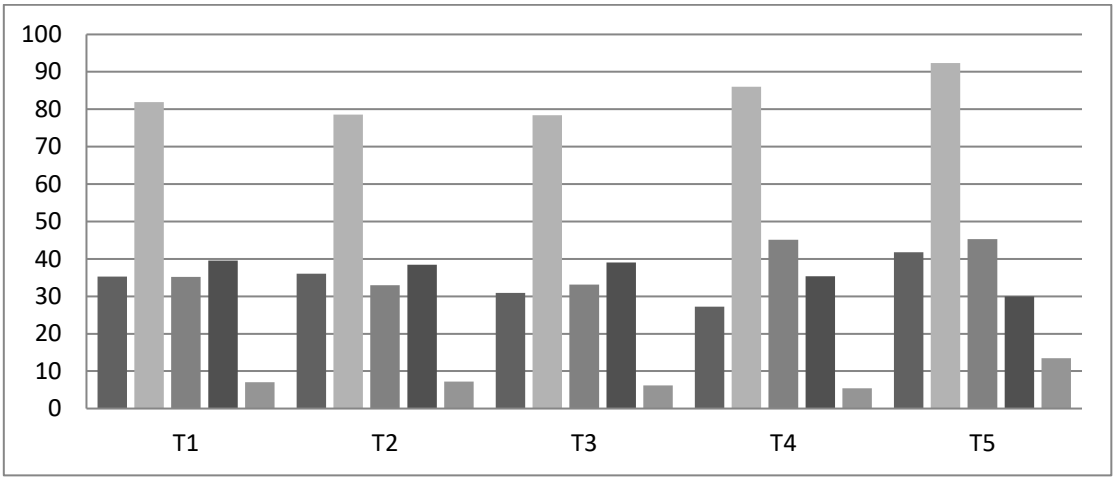

Figure 5. Effects of the treatments on levels of total cholesterol (TC), triglycerides (TG), LDL, HDL, and VLDL in rats. The bar graph shows the mean values (mg/dL) ± SD (n=6 per group). Bars with unlike letters on top differ significantly at $p < 0.05$ (Duncan's test).

4- Discussion

4.1. Body Weight Dynamics

Data showed that there were no significant changes in the body weight of animals in any treatment group over the duration of 28 days for which the study was conducted. Therefore, none of the interventions, including sucrose at the dose administered (10 mg/kg), had any effect on overall energy balance or feed efficiency. The lack of weight gain in stevia-treated groups was as expected since steviol glycosides provide high potency sweetness, not metabolizable calories [16]. It may also be that the age-related metabolic plateau observed in adult rats helps in weight maintenance [17].

Results from our study are in agreement with others in which healthy rodents supplemented with stevia did not experience significant changes in weight [18]. This, however, opposes what has been reported in studies on diabetic or obese models where stevia is associated with weight loss or reduced weight gain. Such discrepancies underscore the importance of metabolic context-healthy versus disease state when extrapolating effects on body composition [19]. A limitation of the present study is the use of healthy, non-diabetic rats, which may not fully represent the metabolic effects in human populations with metabolic syndrome.

4.2. Glycemic Response

The marked effect in glucose reduction by purified steviol glycosides (T2) as opposed to the crude extract (T3) is very important with this study. The PSG group showed a mean FBG of 79.33 mg/dL, while the CAE group showed 127.67 mg/dL. It shows that the isolated active compounds, mainly stevioside and rebaudioside A, are more efficacious in this model than the whole phytocomplex.

Some factors that could explain this variation include whether there is a difference in the bioavailability of steviol glycosides between the purified and crude forms. It is established that purified stevioside is much more readily absorbed in the small intestine. Gut microflora will hydrolyze it to steviol, which is the active metabolite that triggers insulin secretion because it acts on ATP-sensitive potassium channels in pancreatic β-cells. Other

phytochemicals in the crude extract (flavonoids, phenolic acids, chlorogenic acids), however, may be considered since they could competitively inhibit absorption or metabolism of steviol glycosides, thus reducing their efficacy in lowering glucose [20,21]. The other alternative would be whether the active moiety in the purified form was dosed exactly (100% steviol glycosides at 10 mg/kg) to give a consistent pharmacologic effect. While the dose of the crude extract is standardized only to total glycosides, which may contain some nonglycoside compounds that either dilute or interfere with the active compounds.

The insignificant effect of the commercial stevia product (T4) may be related to its formulation. The label by the manufacturer stated that this product contained 99% rebaudioside A; this has a different glycoside profile (higher rebaudioside A-to-stevioside ratio) compared to our laboratory-purified PSG (approximately 2.5:1 stevioside-to-rebaudioside A). Some emerging evidences suggest that different steviol glycosides may have distinct pharmacological potencies. In some models, stevioside is more potent than rebaudioside A in terms of insulinotropic effects [20,21,22]. This underscores the glycocide composition importance in determination of biological activity.

4.3. Hepatic and Renal Safety

All stevia-treated groups (T2, T3, T4) showed ALT and AST values within the normal ranges of healthy rats, which indicates the absence of any hepatotoxicity [23]. The AST value for the PSG group decreased significantly compared to the control group — a finding that could indicate a possible hepatoprotective effect, perhaps through antioxidant mechanisms [24]. The ALT value for the sucrose group increased significantly over the control, reflecting modest metabolic stress on the liver — most likely tied to de novo lipogenesis from fructose metabolism [20].

All renal parameters were within the normal limits with minor but statistically significant fluctuations. Small increases in creatinine were noted at T3, T4, and T5 (0.78-0.83 mg/dL). Since there was no accompanying increase in urea, it is unlikely to show any clinically relevant nephrotoxicity at this level. Non-pathological, transient changes in renal markers at high doses steviol glycoside studies have also been noted. These are considered adaptive physiological responses rather than evidence of toxicity [25]. Such benefits of stevia as improvement in glycemic and lipid control can indirectly provide long-term protection of the kidneys by eliminating major risk factors for chronic kidney disease [26].

4.4. Lipid Profile Modulation

The most significant effect on the lipid profile was observed in the sucrose control group (T5), where levels of TG and TC were significantly higher than those of all other groups. This is in line with the known association between high sucrose intake and dyslipidemia [15]. It does so via the synthesis of triglycerides by the liver and VLDL secretion. All stevia-based treatments, however, showed positive effects on the lipid profile; PSG (T2) and CAE (T3) showed consistent trends toward lower TC, TG, and LDL-C compared to the control.

Steviol glycosides may enhance the clearance of circulating LDL by up-regulating LDL receptors in the liver and increase fecal bile acid excretion, which reduces reabsorption of cholesterol [27,28]. They may also control some important lipogenic enzymes, such as fatty acid synthase and HMG-CoA reductase. The higher LDL-C in commercial stevia (T4) compared to PSG may once more be due to differences in glycoside composition (mainly *rebaudioside A* vs. *stevioside*) or bulking agents, although none was declared on the label. These results agree with previous human and animal studies that have shown that stevia can help maintain healthier lipid parameters than sucrose, thus further supporting its use in foods for cardiovascular health [29,30,31].

4.5. Study Limitations

The study has several caveats. First, the intervention period was relatively short (28 days) to observe long-term metabolic adaptations or chronic toxicity. Second, healthy non-diabetic rats were used so that the results cannot be directly extrapolated to humans with

type 2 diabetes or obesity. Third, the sample size (n=6 per group) is adequate to detect large effects but may not pick up smaller, biologically relevant differences. Histopathological examination of liver and kidney tissues was not carried out in this study; such analyses should be performed in future studies to confirm safety findings. Last, the dose of sucrose (10 mg/kg) is low and not reflective of human consumption; higher doses may lead to more severe metabolic derangements. HPLC data proved the purity of the PSG. The phytochemical composition of the crude extract, i.e., total phenolic content and flavonoid profile, was not characterized. This would impede our ability to identify which impurities may have led to such low levels of activity.

4- Conclusion

The study was to determine the comparative effects of two formulations of *Stevia rebaudiana* in normal rats. The overall results showed that steviol glycosides were more potent in the management of glycemic control since they reduced levels of fasting blood glucose without adverse effects on body weight or safety markers for liver and kidneys. PSG and the crude aqueous extract (CAE) both showed trends in favor of the lipid profile, unlike sucrose, which had a dyslipidemic effect. The commercial stevia product closely resembled purified glycosides in most parameters (e.g., ALT, creatinine) but was less effective in controlling glycemia; thus, this further emphasizes the role that glycoside composition (*rebaudioside A vs. stevioside*) and processing can have on bioactivity. Such results will further substantiate the use of high-purity steviol glycosides with defined ratios of stevioside to *rebaudioside A* as functional ingredients in foods and beverages intended for glycemic and metabolic health. The results also provide a scientific rationale for differentiating stevia-based materials (crude extract vs. purified glycosides) during product development and claims substantiation related to health. Future studies should specifically focus on long-term studies (≥12 weeks) to confirm chronic safety and efficacy, investigations within disease models (e.g., type 2 diabetes, metabolic syndrome, obesity), and well-designed human clinical trials to confirm these findings and establish effective doses for functional food applications. In addition, histopathological examination of liver and kidney tissues and complete phytochemical profile characterization of crude extracts should be recommended for future studies.

Conflict of interest

The authors have no conflicts of interest to disclose that are compatible with the subject matter of this article.

Consent to participate

All authors have expressed their authorization to engage in this publication.

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Ethical Statement

Except for sensory evaluation, we have not conducted any human or animal investigations during this study. Regarding the sensory case.

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