

Detrimental effects of non-centrifugal cane sugar as a substitute for sucrose in sweetened beverages on metabolic and feeding patterns

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Abstract

The demand for healthier sweeteners has increased due to the risk of premature mortality associated with the consumption of sugar-sweetened beverages. Non-centrifugal cane sugar (NCS) appears to be a good option with positive health effects. However, there is no information on the effects of NCS when used as a substitute for sweetening beverages. This work aimed to compare the exposure of *ad libitum* access to NCS and sucrose solutions (SSs). Three groups of *Wistar* rats ($n = 12$) were exposed over 8 weeks to a standard diet and 10% granulated NCS solution (NCS), 10% SS, and water (C). The NCS solution generated the highest drinking intake (142.27 ± 26 mL/day, $p < .05$) among groups. Compared to C (20.61 ± 10 g/day, $p < .05$), NCS and SS significantly reduced their food intake. Of their total caloric intake, 67 (NCS) and 63% (SS) came from the sweetened fluid. NCS and SS developed a larger AC and a higher adiposity index. The highest values for glucose and lipid profile were found in NCS. In conclusion, *ad libitum* access to NCS led to a high, sustained, and escalating drinking pattern, with detrimental health effects. Therefore, it is essential to consider the amount of consumption when recommending functional sweetener products.

Keywords: jaggery; gur; sugar substitutes; feeding patterns; functional food.

Practical Application: This study demonstrated that the amount of consumption of natural sweeteners, such as non-centrifugal cane sugar, should be taken into account when recommending functional sweetener products, since people could perceive this natural sweetener as safe and healthy, which could lead to overconsumption and harmful metabolic effects.

1 INTRODUCTION

Sweeteners are commonly used in beverages and soft drinks. Their high intake has turned sugar-sweetened beverage (SSB) consumption into a growing and worrying public health problem, increasing the risk of metabolic syndrome (MetS) and cardiovascular disease (CVD), the leading cause of mortality worldwide (Pacheco et al., 2024; Tran et al., 2023). The current demand for sugar substitutes and healthier sweeteners is continuously expanding due to growing concerns about the negative impacts of excessive refined sugar consumption. Among the various commercial substitutes, consumers prefer those of natural origin, considering them healthier and safer than processed ones. For example, honey and non-centrifugal cane sugar (NCS) are good options due to their good glycemic index and nutritional value (Iqbal et al., 2020).

NCS is the scientific name given by the Food and Agriculture Organization of the United Nations to an unrefined solid product obtained by intense dehydration of sugarcane juice. Brown in color, it can be found in solid, liquid, and granulated form (Kumar & Singh, 2020). Unlike sugar, whose main composition is sucrose, NCS is composed of sucrose (91.9–95.5%), glucose (2.9–4.6%), and fructose (1.6–3.7%), as well as moisture and water (Alarcón et al., 2021; Ayustaningwarno et al., 2023;

Flórez-Martínez et al., 2023). Its production process allows the retention of minerals (calcium, sodium, magnesium, potassium, phosphorus, iron, zinc, chromium, copper, cobalt, manganese, and selenium), fiber, vitamins (A, B1, B2, B3, B5, B6, B9, C, D2, and E), phenolic compounds (phenolic acids, flavonoids, and anthocyanins), amino acids, fat, and proteins, making it a rich source of nutrients and bioactive compounds. NCS consumption even contributes to daily mineral requirements (Bettani et al., 2024; Iqbal et al., 2017; Kavithani et al., 2024; Pujari, Dedhia, et al., 2024; Zidan & Azlan, 2022). These value-added compositions may be an alternative with positive effects against the harmful effects that refined sugars can generate on health.

NCS is consumed throughout the world and receives different names depending on the geographical location, such as *jaggery* (South Asia, India), *kokuto/kurozato* (Japan), *gur/desi* (Pakistan, India), *khandsari* (South Asia), *muscovado* (Philippines and some African countries), *duong mat mia* (Vietnam), *gula melaka* (Malaysia), *gula merah* (Indonesia), *vollrohrzucker* (Germany), *piloncillo/panocha* (Mexico), *papelón* (Venezuela, Central African countries), *rapadura* (Brazil, Cuba), *panela* (Colombia, Bolivia, Ecuador, Honduras, Nicaragua, Panama), *sweet tapa* (Costa Rica), and *hakura* (Sri Lanka) (Ayustaningwarno et al., 2023; Flórez-Martínez et al., 2021; Thulsasiraman et al., 2023; Zidan & Azlan, 2022). Most of its production is artisanal,

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playing a key role in the local economy and in the diet of populations in South America, the Caribbean, Asia, and Africa. More than 70% of the production of this sweetener is located in India, followed by Colombia (14.9%), Pakistan (5%), China (3.9%), and Brazil (3.7%) (Alarcón et al., 2021; Iqbal et al., 2017; Kavithani et al., 2024; Shrivastav et al., 2016). In India, *jaggery* is known as a “medicinal sugar,” associated with elevation in human life span. In ayurvedic medicine, it has been used to treat infections, bronchitis, cough, anemia, constipation, jaundice, and heart or blood conditions (Hirpara et al., 2020; Seguí et al., 2015). NCS has also exhibited antioxidant, anti-inflammatory, anti-obesity, hypoglycemic, hypolipidemic, antibacterial, immunoprotective, anti-toxicity, anti-anemia, cytoprotective, anticarcinogenic effects, and protective effects against neurodegenerative disease (Seguí et al., 2015; Sharifi-Rad et al., 2023; Zidan & Azlan, 2022).

Despite all the positive biological effects that can be assumed from NCS phytochemicals, its main compounds are simple carbohydrates, essentially sucrose, whose overconsumption could lead to harmful effects, as has been previously demonstrated with the *ad libitum* intake of honey (Martínez-Moreno & Virgen-Carrillo, 2024; Virgen-Carrillo et al., 2021). Furthermore, there is no information about NCS effects when used as a substitute to sweeten beverages. Therefore, the objective of this work was to compare the exposure of *ad libitum* access to NCS and sucrose solutions (SSs) on the feeding pattern, biochemical, and zoometric markers.

2 MATERIALS AND METHODS

2.1 Subjects and habitat

Experiment was carried out in the vivarium of the Instituto de Investigaciones en Comportamiento Alimentario y Nutrición, Mexico after approval by the Ethics Committee of Centro de Estudios e Investigaciones en Comportamiento, University of Guadalajara, Mexico (Ethics protocol number: CUCBA/CEIC/CE/002/2020). Male and female Wistar rats ($n = 36$) were bred and housed in the same location. Experimentally naive, 13–14-week-old rats (weights 250–300 g) were assigned to three experimental groups [$n = 12$, (six males/six females)] using the matched-group design based on body weight (BW). Rodents were single-housed in acrylic cages ($27 \times 37 \times 15$ cm) with hardwood chip bedding and covered by a stainless steel cage top. Bedding was changed every third day or even daily if necessary. Animals were maintained on a 12:12 light/dark cycle (lights on at 07:00) in a climate-controlled colony room ($23 \pm 2^\circ\text{C}$; relative humidity 45%; ventilation rate 15 air changes per hour) (Martínez-Moreno & Virgen-Carrillo, 2024). All experimental procedures were conducted in accordance with the National Institutes of Health in the Guide for the Care and Use of Laboratory Animals (National Research Council et al., 2011).

2.2 Experimental diets and administration procedure

Rats of both sexes were exposed to *ad libitum* diet conditions with LabDiet® Rodent Laboratory Chow 5001 (“standard diet,” composition of 23% protein, 4.5% fat, 6% fiber, 46.5% carbohydrates, 12% humidity, and 8% minerals) plus

different liquid interventions for each group during eight consecutive weeks.

- NCS group: standard diet + 10% granulated NCS solution. The preparation was made using commercial granulated *piloncillo* (NCS; Metco®, Ciudad de México, Mexico), mixed on a weight/volume basis (10 g of powder for every 100 mL of solution).
- SS group: standard diet + 10% SS. The preparation was made using commercial refined sugar (Zulka®, Culiacán Rosales, Sinaloa, Mexico), mixed on a weight/volume basis (10 g of sugar for every 100 mL of solution).
- C group: standard diet + purified water.

For groups NCS and SS, drinking bottles (240 mL plastic bottles with stainless-steel drinking spouts) were filled with sweet solutions instead of simple purified water. These were prepared and replaced daily (every 24 h at 9:00 h) using the corresponding sweetener diluted in purified drinking water, prior to sanitization of the bottle. Group C received purified water in plastic bottles of the same type.

2.3 Feeding pattern and energy intake

Chow and liquid consumption over 23 h for each subject were recorded daily at 8:00 h (the missing hour was used to weigh the food, sanitize, and fill drinking bottles). The feeding pattern was determined from the accumulated bouts over 23 h. For the standard diet, the difference in weight between the provided and the remaining pellets the following day was measured with a precision digital balance (AND GX 2000; A&D Company, San Jose, CA, USA). The liquid ingested was measured by direct observation of the bottle’s measurement scale. Values were expressed in milliliters of liquid (mL) and grams (g) for chow. Recorded food intake in grams was also used to calculate caloric intake. Besides, the feed efficiency ratio was used to determine how kilocalories (kcal) ingested increase BW, as follows: weight gain/total caloric intake (Han et al., 2019). Weight gain was obtained by subtracting the initial BW from the final BW. While total kcal consumed was determined by the sum of food and liquid.

2.4 Zoometric measures

Measurements were made once a week. For BW, a precision digital balance (AND GX 2000; A&D Company, San Jose, CA, USA) was used; and for abdominal circumference (AC) and craniocaudal length (CCL), a plastic measuring tape with an accuracy of 0.1 cm was used, as well as a homemade plastic restriction device to avoid anesthesia. These variables were used to identify obesity with the calculation of body mass index (BMI) as the $\text{BW (g)}/\text{length}^2 (\text{cm}^2)$ (Novelli et al., 2007) and adiposity index (%) as $(\text{total body fat}/\text{final BW}) \times 100$ (Leopoldo et al., 2016). The AC was calculated on the most prominent zone of the abdomen, which was correlated with the weight of adipose tissue (AT), and used it as a predictor of body fat mass *in vivo* (Gerbaix et al., 2010).

2.5 Euthanasia and dissection

On the same day, all rats were fasted and sacrificed rapidly by decapitation under brief CO₂ narcosis (Grupo INFRA[®]; México); immediately a blood sample was collected in Vacutest[®] tubes (KIMA, Arzegrande, Italy). Afterward, bodies were dissected, and AT (subcutaneous, visceral, and epididymal) was isolated and weighed to determine the total body fat with the sum of them (Leopoldo et al., 2016; Virgen-Carrillo et al., 2021).

2.6 Biochemical analysis

Blood samples collected in tubes were incubated (37°C × 30 min) and centrifuged (2,500 rpm × 10 min). Glucose and lipid profile serum analysis were carried out with a dry chemistry technique with a VITROS[®] 250 automatic chemistry analyzer and Micro Slides kits (Ortho-Clinical Diagnostics, Raritan, NJ, USA). The atherogenic index [(AI) = (total cholesterol (TC) - HDL-c)/HDL-c (high-density lipoprotein-cholesterol)] was calculated as previously reported (Seo et al., 2024).

To determine weekly glucose levels, a blood drop sample was collected after pricking the distal end of the tail with a lancet, and the measurement was performed using an Accu-Chek[®] Instant Blood Glucose Meter, Hoffmann-La Roche, Switzerland.

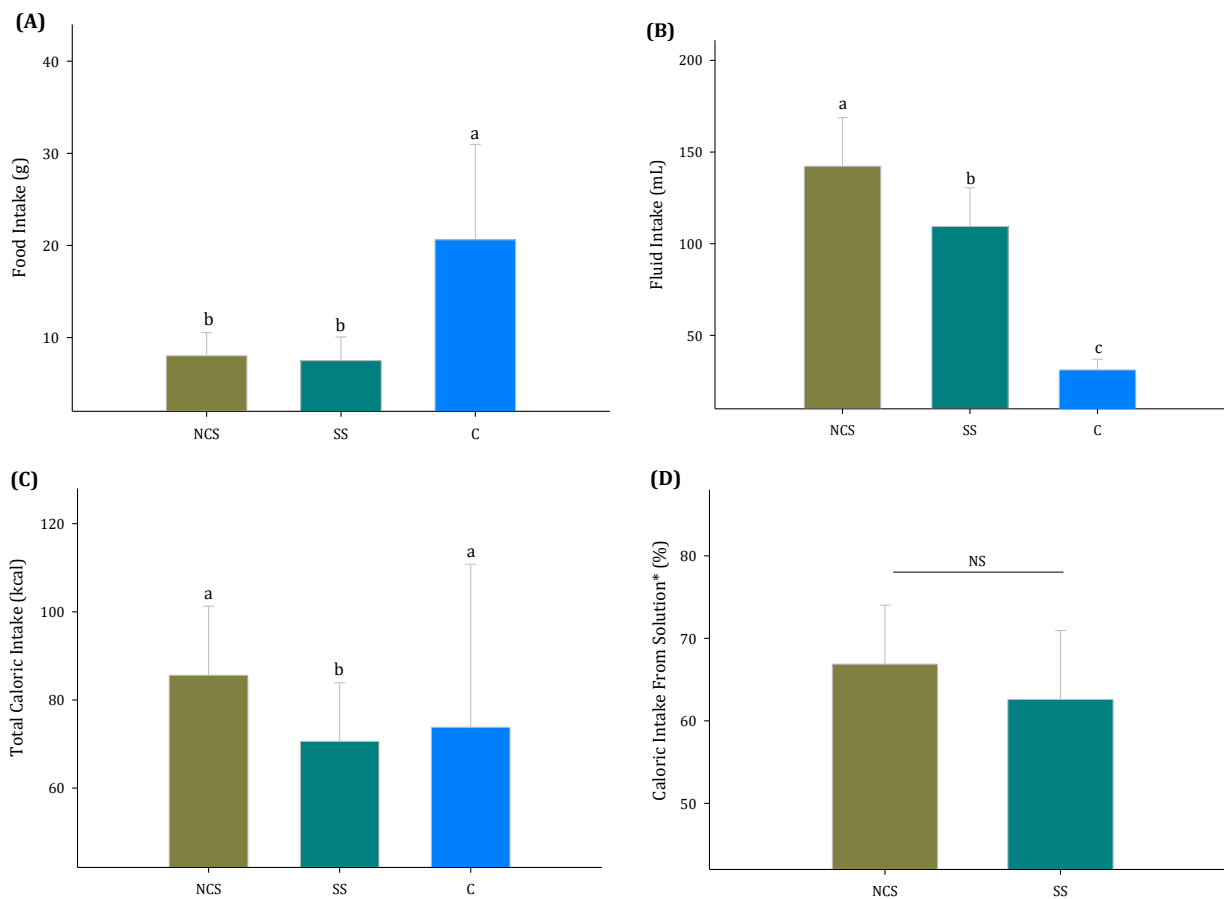
2.7 Statistical analysis

Statistical analyses were performed using SPSS version 24 (IBM[®], Armonk, NY, USA). Normality and homoscedasticity of data were evaluated. Later, one-way analysis of variance followed by Tukey's post hoc analyses was used to determine differences among variables and groups. Significant differences between the NCS and SS groups were determined using Student's t-test. Statistical significance was set and represented as * $p < .05$, ** $p < .01$, and *** $p < .001$. Data are expressed as the mean ± standard deviation. The degree of association was analyzed through the calculation of Pearson's correlation coefficient for quantitative variables, and the interpretation of the correlation size was considered as reported by Mukaka (2012).

3 RESULTS

3.1 Feeding pattern and energy intake

Feeding pattern intake (Figures 1a and 2a) was similar among solution groups with a mean of 8 g/day, while control group consumed a significant difference of 12 g/day more ($p < .05$). *Ad libitum* fluid intake (Figure 1b) was significantly different among groups ($p < .05$). The NCS group consumed 30% more volume of liquid than SS, taking the highest consumption.



*Respect to total caloric intake; NS: no significant difference was found between NCS and SS groups, according to the Student's t-test; **Means with different letters were significantly different ($p < .05$) according to Tukey's test; NCS: non-centrifugal cane sugar solution; SS: sucrose solution; C: control group.

Figure 1. Feeding variables analysis. Values are expressed as mean ± standard deviation ($n = 12$) from the average over 8 weeks.

For the first and second week, the fluid ingestion pattern (Figure 2b) was similar between NCS and SS, with a tendency to increase. However, from the third week to the end of the experiment, the SS group showed a decreasing behavior, significantly reducing its consumption in comparison to NCS ($p < .001$); meanwhile, the last group showed an opposite and escalating consumption behavior. Total caloric intake (Figure 1c) was 20% higher ($p < .05$) in the NCS group compared to the SS. Of this total, the NCS consumed 67% and the SS, 63% of their intake from the sweetened fluid (Figure 1d).

3.2 Zoometric measures

Table 1 summarizes the changes in the variables related to BW. At the end of the experiment, BW was slightly higher in the NCS group ($p > .05$), while the evolution of weight throughout the 8 weeks was similar and consistent with growth between groups (Figure 3a).

The percentage of weight gain over 8 weeks was higher for NCS, followed by SS and C. In spite of this group having the highest total caloric intake (Figure 1c), the feed efficiency was higher ($p > .05$) for the C group (0.81 ± 0.46), followed by SS (0.76 ± 0.31), and the lowest ratio was for NCS (0.69 ± 0.29). At the end of the experiment, BMI among groups did not show significant differences (Figure 3b).

Weight of AT and AC showed a high positive correlation for NCS ($r = .765, p = .004$) and a low positive correlation for SS ($r = .405, p = .191$), while, for the C group, it had a negative and negligible correlation ($r = -.175, p = .586$). Finally, the adiposity index was higher in the solution groups ($p > .05$).

3.3 Biochemical analysis

From the serum biochemical analysis (Figure 4), the results for all the variables evaluated were higher in the NCS group. Final glucose levels were similar among groups (Figure 4a); the levels for NCS were 5 and 11% higher in comparison

with SS and C ($p > .05$). The weekly glucose pattern among solution groups was opposite for many weeks ($p < .05$), with a general tendency to decrease glucose levels in the NCS group and an upward trend in the SS group (Figure 5). The lipid profile (Figure 4b-4e) between NCS and SS did not show any statistical difference; however, in comparison to C, levels were significantly higher ($p < .05$). The AI among groups was similar (Figure 4f).

3.4 Correlations with the solutions intake

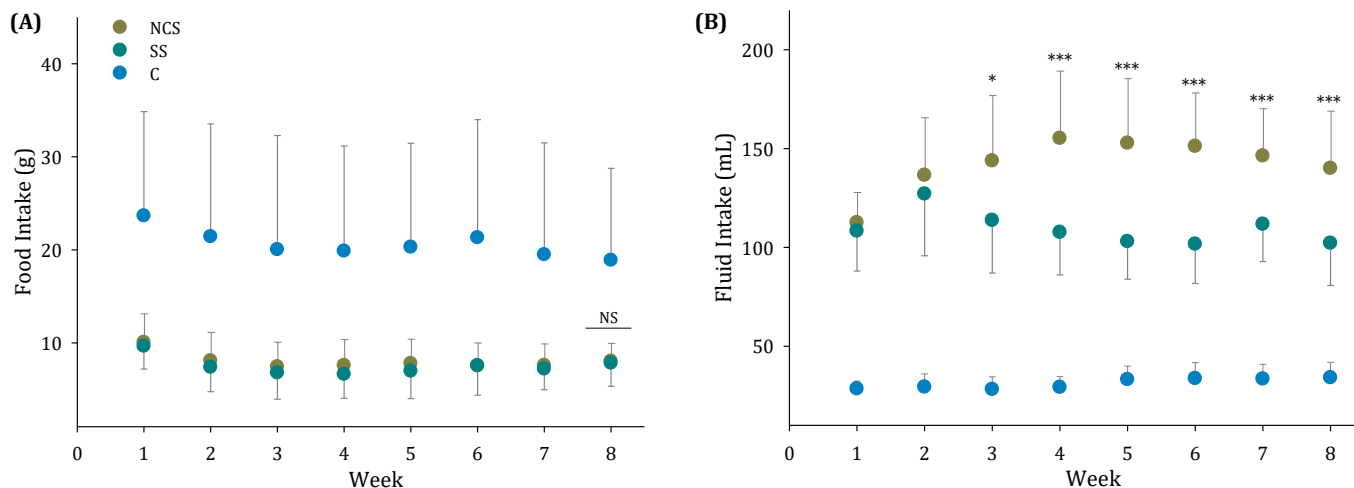
The correlation between sweet solution intake and zoometric and biochemical variables (Table 2) was assessed with the intention of establishing whether *ad libitum* access and the amount of consumption were related to the results observed at the end of the experiment.

For the NCS group, zoometric variables such as weight gain, AT, and adiposity index were low correlated with solution consumption, while biochemical variables such as glucose, total cholesterol, and triglycerides were negative and negligible correlates with fluid intake. In contrast, for the SS group, a moderate and high positive correlation was found for zoometric variables; while a high positive correlation was found for lipid profile and a low positive correlation for glucose levels.

Table 1. Zoometric variables analysis.

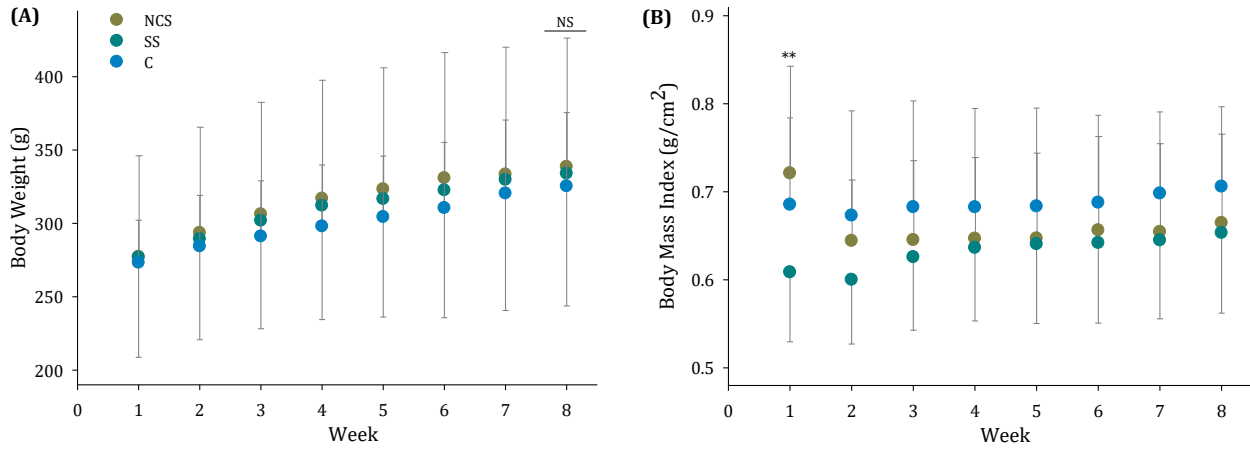
| | NCS | SS | C |
|---------------------------|--------------------------|--------------------------|--------------------------|
| Initial body weight (g) | 277.25 ± 69 ^a | 276.83 ± 68 ^a | 273.25 ± 29 ^a |
| Final body weight | 315.03 ± 79 ^a | 310.40 ± 79 ^a | 300.78 ± 40 ^a |
| % Weight gain (FBW - IBW) | 22.44 ± 13 ^a | 20.10 ± 10 ^a | 18.66 ± 7.8 ^a |
| Final AC | 16.52 ± 1.8 ^a | 16.53 ± 2 ^a | 14.16 ± 1.5 ^b |
| Final BMI | 0.66 ± 0.10 ^a | 0.65 ± 0.09 ^a | 0.70 ± 0.09 ^a |
| Adiposity index (%) | 7.34 ± 2.4 ^a | 7.69 ± 3.4 ^a | 5.74 ± 4.9 ^a |

Values are expressed as mean ± standard deviation ($n = 12$) from the average over 8 weeks; AC: abdominal circumference; BMI: body mass index; FBW: final body weight; IBW: initial body weight; ^{a,b}means with different letters in a column were significantly different ($p < .05$) according to Tukey's test; NCS: non-centrifugal cane sugar solution; SS: sucrose solution; C: control group.



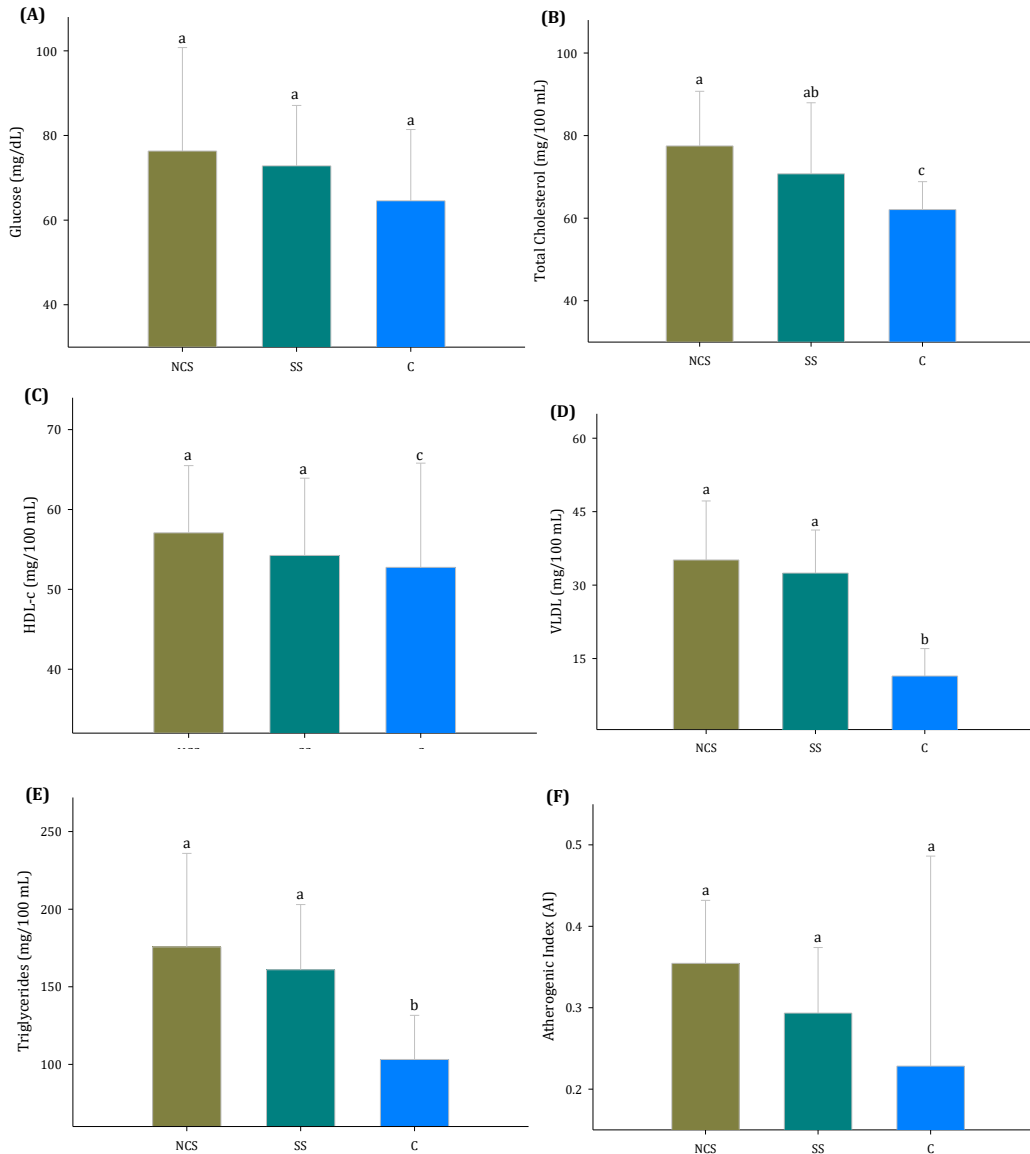
NCS: non-centrifugal cane sugar solution; SS: sucrose solution; C: control group; NS: no significant difference week by week between the NCS and SS groups for food intake, according to Student's t-test; * $p < .05$ and *** $p < .001$ indicate a significant difference week by week between the NCS and SS groups for fluid intake according to Student's t-test.

Figure 2. (a) Feeding pattern of food and (b) fluid intake. Comparison of mean ± standard deviation among groups ($n = 12$) for every experimental week.



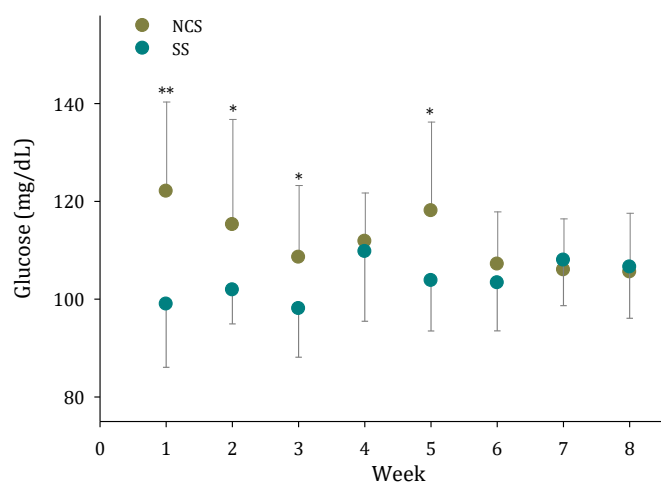
NS: no significant difference week by week between the NCS and SS groups for body weight, according to Student's t-test; ** $p < .01$, indicates a significant difference between the NCS and SS groups for body mass index according to Student's t-test.

Figure 3. (a) Evolution of body weight and (b) body mass index. Comparison of mean \pm standard deviation among groups ($n = 12$) for every experimental week.



^{a-c}Means with different letters were significantly different ($p < .05$) according to Tukey's test; NCS: non-centrifugal cane sugar solution; SS: sucrose solution; C: control group.

Figure 4. Biochemical variables analysis. Values are expressed as mean \pm standard deviation ($n = 12$) from the average over 8 weeks.



* $p < .05$ and ** $p < .01$ indicate a significant difference according to Student's t-test; NCS: non-centrifugal cane sugar solution; SS: sucrose solution.

Figure 5. Weekly glucose pattern. Comparison of mean \pm standard deviation of glucose between the NCS and SS groups ($n = 12$) for every experimental week.

Table 2. Correlations with solution intake.

| Variables | Fluid intake (mL) | | | |
|-------------------------|----------------------|-----------------|---------------------|-----------------|
| | NCS | | SS | |
| | <i>r</i> | <i>p</i> -value | <i>R</i> | <i>p</i> -value |
| Zoometric | | | | |
| Weight gain (FBW - IBW) | 0.3826 ^d | 0.2196 | 0.6699 ^c | 0.0172* |
| Total AT | 0.4813 ^d | 0.1131 | 0.8196 ^b | 0.0011** |
| Adiposity index | 0.3086 ^d | 0.3291 | 0.7692 ^b | 0.0035** |
| Biochemical | | | | |
| Glucose | -0.2356 ^e | 0.4609 | 0.4575 ^d | 0.1348 |
| Total cholesterol | -0.2604 ^e | 0.4138 | 0.7161 ^b | 0.0088** |
| Triglycerides | -0.2118 ^e | 0.5087 | 0.7586 ^b | 0.0042** |

^aVery high positive correlation (0.90–1.00); ^bHigh positive correlation (0.70–0.90); ^cModerate positive correlation (0.50–0.70); ^dLow positive correlation (0.30–0.50); ^eNegligible correlation (0.00–0.30); values with a negative sign indicate the same level of correlation being negative (Mukaka, 2012).

4 DISCUSSION

According to the World Health Organization (WHO, 2022), despite all the recommendations about decreasing sugar consumption, it remains high, exceeding the recommended daily intake. The latest sugar report from the United States Department of Agriculture (USDA, 2024) indicated that in the last 5 years, sugar consumption worldwide has increased year by year.

An effort to reduce SSB consumption has been made with the inclusion of artificially (non-nutritively) sweetened beverages as a “healthier” alternative to caloric intake from SSBs; however, their high consumption is also associated with a higher risk of cardiovascular complications and mortality, even in physically active people (Krittanawong et al., 2023; Pacheco et al., 2024). Recently, the WHO (2023) conducted a systematic review and meta-analysis of randomized controlled trials and prospective observational studies, finding that long-term use of non-sugar sweeteners (low- or no-calorie alternatives) was associated with a higher BMI, obesity, risk of type 2 diabetes, CVD, and mortality in adults.

Although sugar and non-sugar sweeteners are highly contraindicated, evidence on increased sugar consumption indicates that sweet taste is highly sought after by people, given that liking sucrose does not require a learning process since it is a natural reinforcement acquired prior to birth (Ventura & Mennella, 2011). This could be explained by the pleasant taste of sucrose, which, after consumption, generates the release of dopamine, a neurotransmitter involved with pleasure. Dopamine activates the brain's reward pathway, or mesocorticolimbic pathway, a circuit related to motivation and reinforcement. This cerebral action evokes a sensation of pleasure after sugar consumption, which in turn increases the desire for tasty foods and the need for constant activation of the reward pathway, resulting in negative neuroplasticity changes, which contribute to compulsive, addictive, and loss of self-control behaviors (Jacques et al., 2019; Yu et al., 2022).

Aside from the harmful consequences of refined and artificial sugars, people need to satisfy their desire for sweet foods due to their innate preference for them (Ventura & Mennella, 2011); this has led to an increased demand for sugarcane-derived sweeteners that are minimally processed and possess nutritional potential (Bettani et al., 2024). An option is NCS, which, unlike simple, artificial, and processed sweeteners, appears to be safe and recommended for consumption in diabetic patients (Iqbal et al., 2020). Iqbal et al. (2017) found that *jaggery* had a 74% higher concentration of chromium compared with other sugar types. This essential element is often deficient in diabetic people, which results in an important issue to attend to, since it plays a role in insulin regulation and in carbohydrate, protein, and lipid metabolism. On the other hand, unlike sugar, which is absorbed into the blood rapidly and releases energy easily, NCS is made up of longer chains of sucrose, so it is digested slowly, and energy release is also slow (Hirpara et al., 2020; Shrivastav et al., 2016). Recently, Pujari, Pradeep et al. (2024) conducted a clinical trial to compare NCS and refined sugar on blood glucose levels. They found that, unlike NCS, 55% more patients presented a pre-diabetic status when consuming refined sugar than when consuming unrefined sugar. These findings could be related to the delayed absorption of carbohydrates, since they found a strong positive effect on the inhibition of α -glucosidase and α -amylase, which was correlated with the content of bioactive compounds found in NCS.

Several positive aspects have been highlighted in the NCS; however, it seems that the lack of standardization of production processes, the diverse varieties of sugarcane with a wide and non-homogeneous chemical composition, edaphic and agricultural factors, as well as economic and political limitations have been related to a scarce commercialization of this sweetener as a functional food (Aguilar-Rivera & Olvera-Vargas, 2021; Ayustaningwarno et al., 2023; Bettani et al., 2024; Martínez-González et al., 2019; Thulsasiraman et al., 2023). Even the poor storage capacity and shelflife of the product have been mentioned as a limitation (Rao & Singh, 2022).

Despite this, its use as a substitute for sucrose has recently spread to commercial food, bakery, and beverage manufacturing processes to formulate fortified, nutritive, and bio-functional products (Kimura et al., 1984; Martínez-González et al., 2019). Nevertheless, it is important to consider that NCS has a unique flavor and aroma, which varies among products due to the minerals and volatile organic components (Ayustaningwarno et al., 2023;

Flórez-Martínez et al., 2023). For that reason, replacing refined sugar with NCS is complicated due to its organoleptic characteristics and sensory attributes, which could imply an undesired impact and therefore condition consumer acceptance.

In experiments with other natural sweeteners, such as honey, we have found that exposure to free access to a solution containing this sweetener, both in healthy and hyperglycemic rats, resulted in loss of intake control with overconsumption, exceeding daily fluid intake, escalating consumption behavior, and symptoms of illness (Martínez-Moreno & Virgen-Carrillo, 2024; Virgen-Carrillo et al., 2021).

Based on this background, evaluating these effects with other sweetener alternatives was essential. To our knowledge, this is the first report about NCS-free consumption and its impact on feeding behavior and biological effects. A granulated form of NCS was used in this study due to its similarity with the sucrose condition and the advantage in dissolution rate, without affecting its composition (Alarcón et al., 2021). From our results, rodents consumed about 400% more liquid from the sweet solution than rodents that ingested only water; while food intake was the opposite, and the solution groups consumed 40% less chow than the control (Figure 1). This pattern of consumption has been previously reported, where significant sucrose consumption develops, and food intake is reduced (Smail-Crevier et al., 2018). Even when the rodents had pellets to ingest the necessary calories, they preferred to get more than half of their caloric intake from the beverage (Figure 1), probably to compensate for the calories consumed through the sweetener.

Similar to the results observed in other experiments, we found that rodents prefer the taste of sucrose over other sugars (Sclafani & Mann, 1987); however, this is the first time that an experiment employs an NCS solution and evaluates ingestion. In this study, we observed that the intake pattern of the NCS group was superior to that of the SS group, and their consumption increased weekly, demonstrating escalating intake behavior (Figure 2b); which could be associated with the intake period, since it has been shown that rodents exposed to unlimited access of sweetened solutions for 24 h have ingested the liquid in generally inactive periods (Avena et al., 2008).

In relative to zoometric variables, although rodents exposed to NCS increased BW slightly more, the final adiposity index was slightly lower in them. In rodents exposed to a 10% brown sugar solution (a centrifuged form of cane sugar), it has been observed that consumption of this solution resulted in lower body fat mass than those exposed to a SS (Sánchez-Tapia et al., 2020), and lower BW than other sweeteners, such as sucrose, fructose, glucose, or sucralose (Sánchez-Tapia et al., 2019). This was probably due to the fact that rats fed brown sugar developed smaller adipocytes than those fed sucrose (Sánchez-Tapia et al., 2019). Similarly, Shamsi-Goushki et al. (2020) exposed rodents to a 15% sugar solution by oral gavage for 42 days, finding that those exposed to brown sugar developed lower BW.

The effects of NCS on biochemical variables have been previously explored. In diabetic conditions, Anjum et al. (2021) found that alloxan diabetic rats exposed to *jaggery* (1g/kg bw by oral gavage) for 28 days developed the highest glucose levels (134.5 mg/dL) among the honey, cane sugar, and control groups. Meanwhile, Sánchez-Tapia

et al. (2019) demonstrated that a 10% brown sugar solution (a centrifuged form of cane sugar) administered to rodents fed a high-fat diet for 4 months had lower glucose levels than those exposed to other sweet solutions containing sucrose, fructose, glucose, or sucralose.

Okabe et al. (2009) demonstrated the antiatherosclerotic function of phenolic compounds from *kokuto* in Japanese quail fed an atherosclerotic diet and sucrose, or different types of *kokuto* (NCS). Their results indicated that intake of NCS prevented the development of atherosclerosis. While Kimura et al. (1984) found that rodents fed a high-sugar diet and the non-sugar fraction of crude black sugar (500 or 1,000 mg/kg/day of BW) for 61 days had lesser elevations in serum triglycerides, lipid peroxides, and insulin.

From our results in biochemical analysis, we found the highest levels of glucose and lipid profile after consumption of NCS. We assumed that it was directly related to the amount of consumption, even when it was not correlated by the Pearson's correlation coefficient test. However, the glucose pattern assessed each week showed a tendency to decrease glucose levels in almost all experimental weeks (Figure 5), which could imply a positive effect of NCS intake through slower ingestion and energy release due to their longer chains of sucrose (Hirpara et al., 2020).

Similar to our findings, Anjum et al. (2021) did not find any beneficial effects of *panela* when administered to diabetic rodents. However, the limited availability of evidence, both from *in vivo* studies and clinical trials, makes it difficult to reach a consensus on the results and, therefore, their clinical applicability. Another aspect to consider is the lack of rigorous and scientific evidence that supports the health effects of NCS bioactive compounds and the pathways of action (Pujari, Pradeep, et al., 2024). From the above, more research is needed to clarify the positive biological effects of NCS as a functional food and as an element in the development of nutraceuticals for the prevention and management of disease. An important challenge is the standardization of processing conditions and quality in order to ensure that the nutritional composition, bioactive compounds, and sensory characteristics of the sweetener are homogeneous. Additionally, since the type and quantity of phytochemicals are responsible for the functional properties of foods, a limitation to our research was not having determined the quantity and composition of phenolic compounds present in the NCS used, since they can vary due to agronomic factors and industrial processing conditions; for example, the thermal process and temperature variations to obtain NCS product decrease content of bioactive compounds (Cifuentes et al., 2021; Zidan & Azlan, 2022).

Otherwise, due to the fact that the ingestion of palatable substances could develop a binge drinking behavior (Avena et al., 2008), in the case of using NCS as a substitute for sucrose in sweetened beverages, it is important to take into account diverse aspects such as its organoleptic characteristics and the amount of consumption, since with the *ad libitum* ingestion protocol, we have demonstrated once again that this sweetener also generates overconsumption when access is not conditioned and limited. Our findings support the hypothesis that, despite the diverse chemical composition, organoleptic characteristics, and metabolic process of NCS intake, its consumption could be activating brain reward circuits and generating unhealthy effects, similar to those exerted by sucrose. In spite of the widely

recommended use of natural substitutes of sucrose, such as NCS, we strongly suggest the incorporation of warning messages, since humans usually regulate food intake based primarily on satiety and satiation cues (García-Flores et al., 2017) and could perceive this natural sweetener as safe and healthy.

In conclusion, our findings showed that rodents with unlimited access to NCS developed the highest solution intake, with a sustained and escalating drinking pattern throughout the experiment. From these results, the amount of consumption of natural sweeteners, such as NCS, should be taken into account when recommending functional sweetener products.

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