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Acceptability and tolerability of a *Hibiscus sabdariffa* L. beverage and effect on biomarkers of pregnant women: Phase I pilot trial

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Submission date: September 7th, 2025; **Acceptance Date:** November 4th, 2025, **Publication Date:** November 10th, 2025

Please cite this article as: Alcantar-Rodríguez V.E., Osorio-Díaz P., González-Vargas E., Puga-Díaz R., Gutiérrez-Trujillo J., Saldo-Periago J. Acceptability and tolerability of a *Hibiscus sabdariffa* L. beverage and effect on biomarkers in pregnant women: Phase I pilot trial. *Functional Foods in Health and Disease.* 2025; 15(11):841 – 853.
DOI: https://doi.org/10.31989/ffhd.v15i11.1768

ABSTRACT

Background: Hibiscus sabdariffa L. (HS) is a plant in the Malvaceae family, known as roselle, whose calyces contain compounds with antioxidant and anti-inflammatory properties. Various studies have demonstrated its antihypertensive, antihyperlipidemic, and glycemic control effects. During pregnancy, women also experience metabolic and biochemical changes that allow them to adapt to the development of a new human being. Among these metabolic changes are increased plasma concentrations of glucose and fatty acids, which can serve as substrates for fetal growth. However, if not adequately controlled, they can lead to gestational diabetes and dyslipidemia. One of the main complications of pregnancy is hypertensive disorders, which affect 10% of worldwide pregnancies and are the leading cause of maternal and fetal morbidity and mortality.

Objective: This work aimed to evaluate the acceptability and tolerability of a Hibiscus sabdariffa beverage and its effect on biomarkers in women in the second trimester of pregnancy.

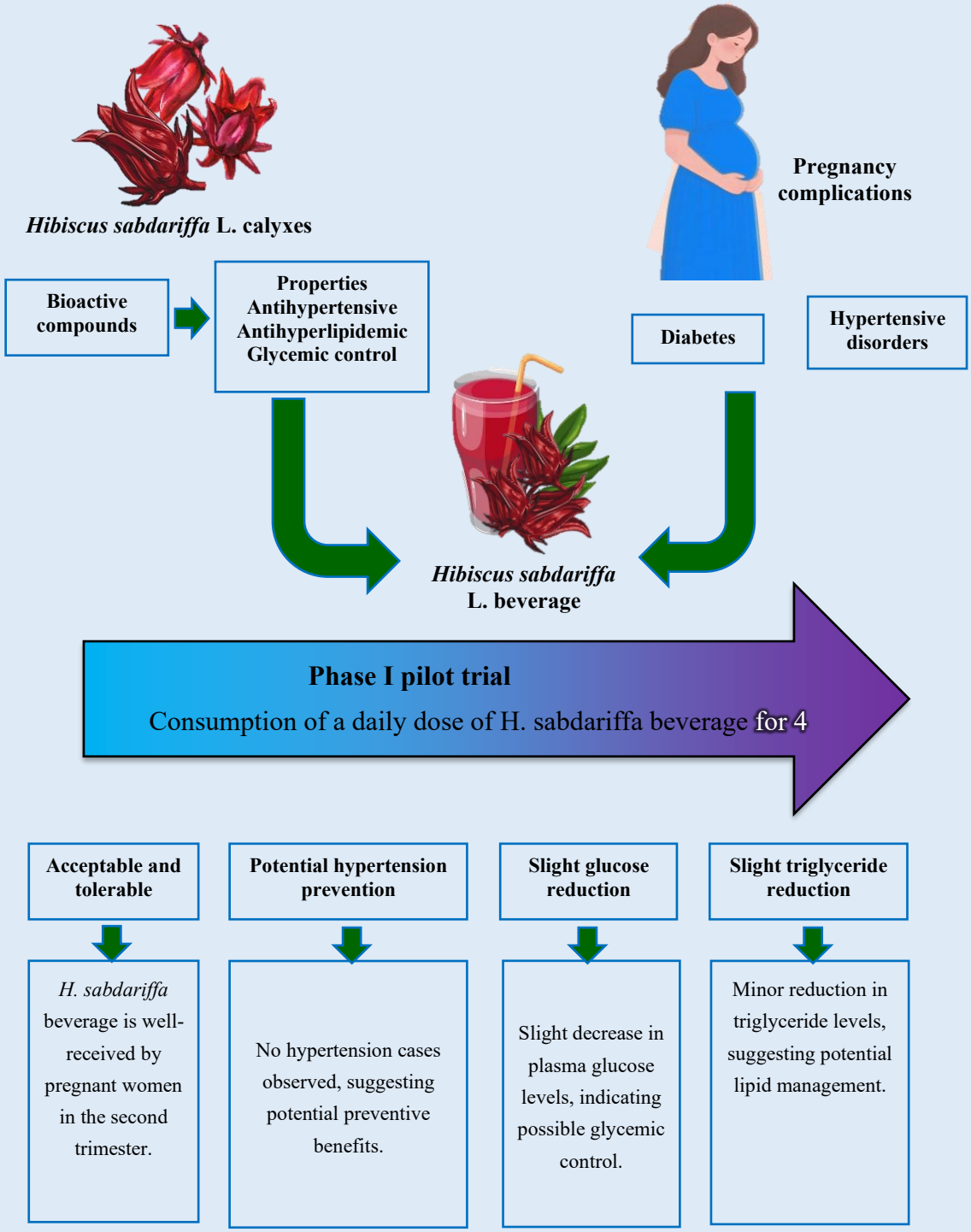
Methods: A four-week phase I pilot trial was conducted in women in their second trimester of pregnancy. Participants consumed a daily dose of HS beverage, which provides 9.6 mg of total anthocyanins, and several metabolic parameters were recorded (diastolic and systolic blood pressure, plasma glucose, cholesterol, triglycerides, and creatinine concentrations, as well as urinary protein levels). Measurements were taken before the start of the trial and at the end of the 4 weeks following beverage consumption.

Results: The protocol for this study was approved by the Research Ethics Committee of the Centro de Desarrollo de Productos Bióticos. Ten women participated in the trial. Diastolic and systolic blood pressure values did not change significantly between the initial and final measurements. Plasma markers also showed no significant differences between the two measurements, although there was a slight decrease in glucose (from 80.5 ± 8.4 to 74.8 ± 9.6 mg/dL) and triglycerides (from 110.7 ± 24.5 to 105.7 ± 14.4 mg/dL). The limitations of this work were the number of participants and the study time, however, as it was a phase I pilot trial, the aim was to identify the acceptability and tolerability of the beverage and to obtain preliminary information regarding the biomarkers to apply them in a study with a larger number of participants over an extended period.

Novelty: The originality of this work is the use of an HS beverage made from ground calyces, instead of a traditional infusion or extracts, to determine whether its use is feasible during pregnancy, as well as to obtain preliminary information about its effects on blood pressure and biomarkers. This pilot is the first to evaluate a ground-calyx Hibiscus sabdariffa beverage (not an infusion or extract) providing 9.6 mg/day total anthocyanins specifically in second-trimester pregnant women, focusing on acceptability, tolerability, and preliminary cardiometabolic biomarkers.

Conclusion: HS beverage demonstrated acceptability and tolerability. Although the number of women included in this preliminary trial is low, it may be expected to have at least one case of an increase in blood pressure, but none presented these symptoms. The prevention of hypertension in all cases is a promising result. The HS beverage could be evaluated in longer-term clinical trials to confirm the maintenance of blood pressure and biochemical indicators at adequate values for pregnant women according to World Health Organization throughout the pregnancy.

Key words: Hibiscus sabdariffa, acceptability, tolerability, hypertensive disorders of pregnancy



Graphical Abstract: Acceptability and tolerability of a Hibiscus sabdariffa L. beverage and effect on biomarkers of pregnant women

INTRODUCTION

Hibiscus sabdariffa L. (HS), commonly known as roselle, is a plant distinguished by its content of phenolic compounds, particularly anthocyanins and flavonoids [1]. Due to its properties, it is used for medicinal purposes [2]. In Mexico, HS consumption is widespread. The calyces of this plant are used for culinary purposes, mainly in the development of beverages [3]. Due to its richness in bioactive compounds, HS has demonstrated therapeutic uses as an antioxidant, antidepressant, diuretic, antihyperlipidemic, antiobesity, hepatoprotective, and antihypertensive, as well as for glucose control [4]. Regarding its antihypertensive effect, this has been demonstrated in different populations [5] but not in pregnant women. The proposed mechanisms by which HS reduces blood pressure include vasodilation, a diuretic effect, and reduced angiotensin II by inhibiting angiotensin-converting enzyme, mechanisms attributed mainly to its anthocyanin content [6]. According to Herrera-Arellano, 9.6 mg of anthocyanins is the dose that affects blood pressure control [7]. Since consuming HS beverages is a traditional practice in Mexico, this cultural acceptance can be leveraged to develop a functional beverage with bioactive compounds that offer them additional health benefits beyond basic nutrition [8]

10% of worldwide pregnancies suffer from some form of hypertensive disorder, causing problems that put the mother's and fetus's life at risk. Among pregnancy-related hypertensive disorders, preeclampsia is estimated to impact 5-7% pregnancies worldwide [9]. It is responsible for more than 500,000 perinatal deaths and 70,000 maternal deaths per year [10]. Drug therapy for hypertensive disorders has adverse effects [11]. Because of this, alternatives are being sought in natural products that control blood pressure without adverse effects [12]. Among these alternatives, functional foods can be used, which provide health benefits beyond nutrition due to their bioactive compounds [13].

Pregnancy is characterized by hormonal changes that influence sensory perception, particularly taste and smell [14–15]. Despite its relevance, this area remains underexplored, with much of the existing knowledge being anecdotal or empirical in nature [16]. However, recent studies have begun to investigate these phenomena more rigorously. For instance, Matsuda et al. proposed that oxytocin may modulate olfactory sensitivity in pregnant women [17]. Similarly, Muluh et al. provided moderate evidence of sensory alterations during pregnancy, including a diminished ability to identify odors, changes in odor intensity perception, and shifts in hedonic responses to flavors [14].

The assessment of acceptability and tolerability is an essential component in the development of foods and beverages with potential health benefits, as it helps ensure their safety and optimize their acceptance by the target population, which seeks healthy products without compromising flavor [18]. These analyses facilitate adjustments to the formulation to promote adherence to the proposed therapeutic use. Acceptability can be determined through sensory analysis [19], with consumer-oriented tests being the most effective for identifying product attributes that elicit the greatest liking or disliking.

In this work, a phase I pilot test was carried out, which consists of testing on a smaller scale the execution logistics planned for a higher-level project and thereby reducing the probability of errors in future studies [20] to evaluate the acceptability and tolerability of an HS beverage, as well as its effect on biomarkers in pregnant women. Indicators such as blood pressure, glucose, cholesterol, triglycerides, and creatinine, as well as a urine test, were evaluated. This trial was conducted in pregnant women because this is the target group for the

beverage and because physiological changes during this stage alter food sensory perception [14].

MATERIALS AND METHODS

A 4-week phase I pilot trial was conducted in women in the second trimester of pregnancy, in accordance with the ethical principles of the Declaration of Helsinki. This work was approved by the Research Ethics Committee of the Centro de Desarrollo de Productos Bióticos of the Instituto Politécnico Nacional, México (2024-1 CEI-CEPROBI) and registered in ClinicalTrials.gov (NCT07175597). The acceptability and tolerability of an HS beverage were measured, as well as the effects on blood pressure and biomarkers.

Subjects: Participants were recruited from the gynecology department of the MEDOMAI clinic in Cuernavaca, Morelos, Mexico. They signed the informed consent form and were selected according to the inclusion and exclusion criteria presented in Table 1. This study did not have a control group; each participant served as their own control, with values measured before and after consumption of the beverage.

Table 1. Inclusion and exclusion criteria used to select participants.

Inclusion criteria	Exclusion criteria
- Age 18 to 35 years	- Multiple or high-risk pregnancy
- Second trimester of pregnancy (14–28 gestational weeks)	- Having suffered from a hypertensive disorder in previous pregnancies
- Adequate blood pressure (<140/90 mmHg)	- Having chronic non-communicable diseases
	- BMI ≥ 32 kg/m²
	- Taking medications that increase blood pressure

Hibiscus sabdariffa L. beverage: The calyxes used to prepare the HS beverage were obtained from the Sabeamor company in the state of Morelos, Mexico. The calyxes were dried at room temperature in a darkroom and then ground in a mill model MC 200 from Encapsuladoras México®. The anthocyanin content was measured by the differential pH method [21], to determine the amount of HS powder that provides 9.6 mg of anthocyanins, as according to Herrera-Arellano et al., it is the amount that affects blood pressure control [7]. Preliminary tests were carried out at the laboratory level to develop the proposed beverage, which was finally composed of 5.7 g of HS powder, 5 g of sugar, and 250 ml of water. Microbiological analyses of the beverage were within the permissible limits according to Mexican regulations (NOM-218-SSA1-2011).

Acceptability and adherence to Hibiscus sabdariffa beverage consumption: The acceptability of the beverage was assessed through sensory analysis with questionnaires applied once a week for 4 weeks using a 7-point hedonic scale, which evaluated the attributes of color, odor, flavor, mouthfeel, aftertaste, and general appearance. Scoring was as follows: 1 = I dislike it a lot, 2 = I dislike it moderately, 3 =I dislike it a little, 4 = I neither like it nor dislike it, 5 = I like it a little, 6 = I like it moderately, and 7 = I like it a lot. In this same questionnaire, participants were asked about their attachment to the beverage, whether they had consumed it, and the approximate amount (100, 75, 50, or 25%).

Hibiscus sabdariffa L. beverage tolerability: Once a week for the 4 weeks of the trial, participants completed a questionnaire to assess gastrointestinal tolerability as proposed by De Luis *et al*. [22]. They reported the presence or absence of gastrointestinal symptoms such as nausea, regurgitation, vomiting, constipation, diarrhea, flatulence, and abdominal pain. Participants

could report if the symptom was absent, if the symptom was present but not bothersome, if the symptom was bothersome but did not interfere with daily activities or sleep, if the symptom was present interfered with daily activities and sleep, or if the symptom was present and required medical attention.

Blood pressure and biochemical markers: Blood pressure, as well as biochemical markers of serum glucose, cholesterol, triglycerides, creatinine, and proteinuria, were measured before the start of the trial and after the 4-week beverage consumption period ended.

Statistical analysis: The results were analyzed using SPSS software through paired analysis to determine statistical differences between the indicators measured before and after treatment, with a significance level of $p<0.05$. In addition, descriptive statistics, including averages and percentages, were used to characterize the group.

RESULTS

Participants selection: Figure 1 presents the flow diagram of participants in the pilot trial.

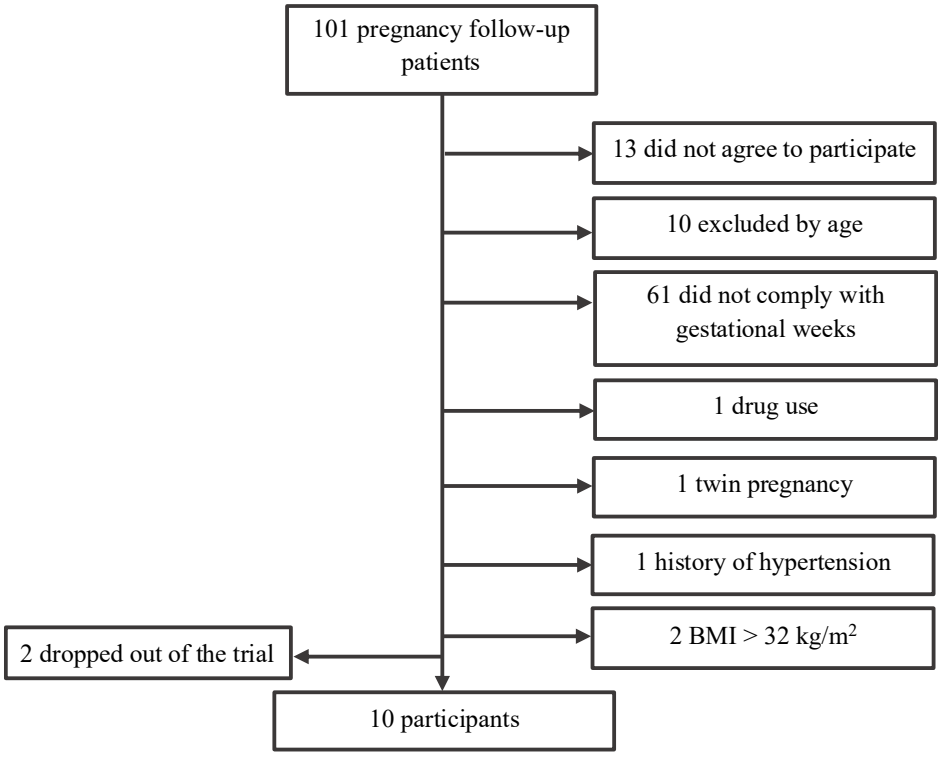


Figure 1. Participant flowchart of phase I pilot trial.

As shown in Figure 1, 12 participants were selected for the trial; however, 2 voluntarily withdrew, and 10 completed the study. The mean age of the participants was 26.4 years, and the mean gestational age was 20.6 weeks.

Hibiscus sabdariffa beverage adherence: The beverage enjoyed strong adherence, with an average consumption rate of 98% in the first week, which decreased to 87% and 84% in the second and third weeks, respectively, and increased to 91% in the fourth week. The average consumption rate for the four weeks was 90%.

Hibiscus sabdariffa beverage acceptability: The *H. sabdariffa* beverage acceptability results are shown in Figure 2.

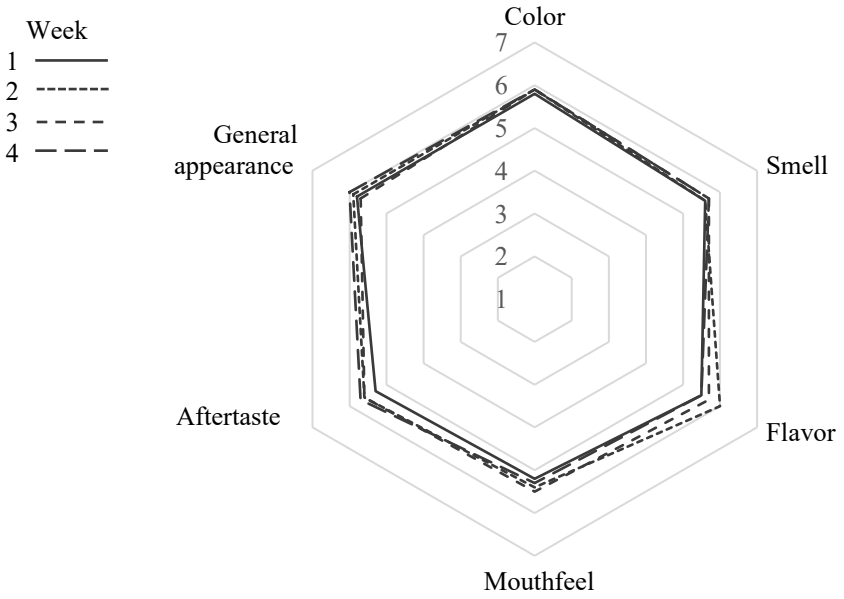


Figure 2. Sensory evaluation of the *Hibiscus sabdariffa* L. beverage per week.

As shown in Figure 2, there was little variation in sensory perception across all attributes evaluated for the beverage over the course of the four weeks of consumption. For all aspects evaluated, the scores ranged from 5 to 6, corresponding to “I like it a little” to “I like it moderately”.

Hibiscus sabdariffa L. beverage tolerability: The results of the symptoms reported by participants, attributed to beverage consumption, are presented in Table 2.

Table 2. Gastrointestinal symptoms reported by participants due to the consumption of the beverage per week.

Week	Nausea	Regurgitation	Vomit	Constipation	Diarrhea	Flatulence	Abdominal pain
1	😀😀	😀		😀😀	😀	😀😀	😀😀
2	☹	😀😀	☹	😀😀☹	😀	😀	😀😀😀
3	😀🩹	😀	😀	😀😀☹	😀☹	😀😀	☹
4	😀	😀	😀	😀😀☹	😀☹	😀😀	

😀 Present but not bothersome ☹ Present and a little annoying, but does not interfere with activities
🩹 Present and annoying, because it interferes with activities 🚑 Requires medical attention.

The most frequently reported symptoms among participants were constipation, diarrhea, and flatulence, followed by nausea, abdominal pain, and regurgitation. The least commonly reported symptom was vomiting. Most reported symptoms were present and not bothersome, and very few were mildly bothersome but did not interfere with daily activities or sleep. Only one patient reported nausea that was bothersome because it

interfered with her activities, and no patients reported any symptoms that required medical attention during the four weeks.

Blood pressure and biochemical indicators: The results of participants' measurements before the trial and after 4 weeks of HS beverage consumption are presented in Table 3.

Table 3. Blood pressure and biochemical indicators before and after beverage consumption.

Indicator	Before	After	*p-value*
Systolic blood pressure (mmHg)	92.8 ± 7.0	94.5 ± 7.3	0.51
Diastolic blood pressure (mmHg)	72.3 ± 5.7	73.3 ± 4.7	0.59
Glucose (mg/dL)	80.5 ± 8.4	74.8 ± 9.6	0.11
Cholesterol (mg/dL)	168.0 ± 24.2	174.7 ± 33.0	0.47
Triglycerides (mg/dL)	110.7 ± 24.5	105.7 ± 14.4	0.54
Creatinine (mg/dL)	0.6 ± 0.07	0.6 ± 0.09	0.50
Proteinuria cases (average mg/dL)	5+ (22.5)	4+ (15)	--

As shown in Table 3, there was no significant difference between the indicators measured before and after consuming the HS beverage. The indicators that increased, although not statistically significant, were systolic and diastolic blood pressure, and cholesterol, while glucose and triglycerides decreased. The number of participants with proteinuria also decreased, as did the average concentration of positive cases. Creatinine values remained unchanged.

DISCUSSION

One limitation of this work was the small number of participants; however, as this was a Phase I pilot trial, the purpose was to obtain safety information on the beverage to determine whether it was acceptable and tolerable to support its consumption in a larger trial. Despite starting from a population of 101 candidates, when applying the inclusion and exclusion criteria, 90% were discarded. The main reason for not including them in the study was that they were not within the gestational weeks specified in the inclusion criteria (61 participants). This happens as most of the candidates go to a gynecology consultation in the final stages of their pregnancy, and this coincides with what was reported by Garza-Elizondo *et al.,* indicating that less than 25% of pregnant women go to prenatal care in Mexico [23].

The average adherence to beverage consumption over the 4 weeks was high, at 90.2%. There are few studies in pregnant women that evaluate adherence to treatment, and those that exist correspond to dietary and physical activity treatments, where it has been reported that adherence may decrease toward the end of pregnancy [24]. But adherence is higher when there is constant monitoring [25], as was the case in this work, which, in addition to lasting only one month, also included weekly contact with the participants. Participants reported that the main reason for treatment detachment was forgetfulness, not displeasure with the beverage, which is consistent with the results of the sensory evaluation.

The beverage demonstrated acceptability because the average of the attributes evaluated were on the scale of, “I like it a little” and “I like it moderately,” and this likeliness was maintained during the 4 weeks evaluated. Mouthfeel and aftertaste attributes were assessed individually with an evaluation of displeasure by few participants, but in all cases the rating was I dislike it a

little. No attribute was evaluated with I dislike it moderately or I dislike it a lot during the 4 weeks.

Most of the symptoms reported by participants to assess the tolerability of the beverage were present but not bothersome. During the 4 weeks, 8 cases were reported as slightly bothersome but did not really interfere with daily activities or sleep among the 7 symptoms surveyed. Only one case was presented during the 4 weeks of a participant who reported nausea that was bothersome because it interfered with daily activities. Although nausea usually ends in the first trimester, there are reports of cases where it persists until the later stages of pregnancy [26]. The most frequently reported cases were constipation and diarrhea, which are attributed to progesterone, which relaxes the gastrointestinal muscles and thus decreases motility [27]. On the other hand, abdominal pain may be due to the growth of the uterus, which compresses the stomach and intestine [28]. The tolerability of the drink was demonstrated because reports of symptoms were few and generally harmless, although these could be attributed to pregnancy-related conditions.

In the indicators measured before and after 4 weeks of consumption of the beverage presented in Table 3 the changes were not significant, as previously mentioned. In the case of blood pressure, there was a slight increase in systolic and diastolic pressure from 92.8 ± 7.0 to 94.5 ± 7.3 mmHg and from 72.3 ± 5.7 to 73.3 ± 4.7 mmHg, respectively, which can be considered normal because the blood pressure gradually increases from the second trimester to the end of the pregnancy [29]. However, in the early stages of pregnancy, blood pressure decreases due to reduced vascular resistance [30], which was precisely the stage in which the participating women were at the beginning of this study. Another study that confirmed the findings of this trial evaluated blood pressure in healthy pregnant women in Mexico City as gestation progressed and found that the lowest blood pressure values were recorded at the beginning of the second trimester, increasing as gestation progressed into the third trimester [31].

In our study, cholesterol concentration increased from 168.0 ± 24.2 to 174.7 ± 33.0 mg/dL, which was not statistically significant ($p>0.05$); however, the values remained within the appropriate limits according to the WHO. It has been suggested that changes in the lipid profile during pregnancy result from metabolic adaptation to the fetus's needs [32]. Lipids generally increase as pregnancy progresses to meet the energy and biosynthetic demands of the mother and fetus. [33]. Bañuelos-Martínez et al. found an increase in cholesterol concentrations between the second and third trimester of pregnancy in women of 143 mg/dL in the second trimester. They increased to 198 mg/dL in the third trimester of pregnancy [34], increasing by 38% while in our study, the increase was 11%.

The glucose and triglyceride levels of the participants in this work decreased at the end of the 4 weeks of consumption of the beverage from 80.5 ± 8.4 to 74.8 ± 9.6 and from 110.7 ± 24.5 to 105.7 ± 14.4, respectively, without being statistically significant ($p>0.05$). This decrease may be related to the consumption of HS, since it has been reported that its consumption causes a reduction in glucose [35] and triglycerides in other groups than pregnant women [36-37].

The effect of HS on lowering glucose levels has been demonstrated in murine model studies [38]. Although murine models are generally used to establish initial safety, they present physiological and metabolic differences that may limit their applicability to humans. Therefore, human studies allow for determining efficacy, bioavailability, dosage, and adverse effects in the target population under real-world conditions [39]. The hypoglycemic effect of HS has also been reported in humans; one study demonstrated a decrease in postprandial blood glucose levels after HS extract consumption [38].

Regarding the slight decrease in triglycerides found in this work, it has also been reported in a study where a triple-blind randomized clinical trial which was conducted in 72 obese adolescent patients who were given a dose of HS powder (6 g) very similar to the one we gave in this work (5.7 g) during the same time of this work (4 weeks) and they observed the decrease in triglycerides [40]. In another study, it has been suggested that polyphenols of HS have lipase inhibitory activity, which decreases the digestion of lipids that are consumed together [41]. The antihyperlipidemic effect of HS can also be attributed to anthocyanins and protocatechuic acid, which, together with isomers of hydroxycitric acid, inhibit the citrate lyase enzyme, thereby reducing the generation of acetyl-CoA and, consequently, the biosynthesis of triglycerides [36].

Creatinine is a marker of interest in pregnancy that is even used as a predictive marker for preeclampsia [42]. The increased concentration causes kidney damage, which causes an increase in the concentration of creatinine in urine. It has been observed that women who develop preeclampsia have an elevated creatinine concentration [43]. The appropriate values for pregnant women are between 0.4 and 0.8 mg/dL, which correspond to the values found in this work, which did not change with respect to the consumption of HS beverage, with 0.6 ± 0.07 mg/dL in the initial measurements and 0.6 ± 0.09 mg/dL in the final measurements.

In the case of proteinuria which is also used as a predictive factor for the development of preeclampsia, according to the results shown in Table 3, before consumption of the beverage 5 participants had protein in urine and the average of protein excreted in urine was 22.5 mg/dL and after 4 weeks of consumption of the beverage there was a reduction in the number of cases from 5 to 4 and of these 4 cases the average amount excreted was also reduced by 15 mg/dL. However, in both cases, the amounts excreted do not represent a risk for the development of preeclampsia.

Scientific Innovation: We operationalized a food-form intervention suitable for real-world use in pregnancy and tracked blood pressure, glucose, triglycerides, cholesterol, creatinine, and urinary protein pre/post over 4 weeks. Although no significant changes were observed (N=10), the absence of BP elevations and directionally lower glucose and triglycerides offer feasibility signals to power a larger, longer trial with dose–response and comparator arms.

Practical Implications: If confirmed in adequately powered studies, a standardizable, palatable HS beverage could become a low-cost, food-based option to help maintain healthy blood pressure and metabolic profiles during pregnancy, complementing routine prenatal care. Next steps include longer duration, larger sample size, anthocyanin dose optimization, and safety/efficacy monitoring aligned with WHO guidance for pregnancy.

CONCLUSIONS

The HS beverage demonstrated acceptability and tolerability, which promotes its use during pregnancy. Although the number of women included in this preliminary trial is low, it may be expected to have at least one case of an increase in blood pressure due to the worldwide prevalence of hypertensive disorders, which did not appear. The prevention of hypertension in all cases is a promising result. The HS beverage must be evaluated in longer-term clinical trials with a large number of subjects to prove the maintenance of blood pressure and biochemical indicators at adequate values for pregnant women according to WHO.

Limitations: This study is limited by being a phase I pilot trial, which is why the number of participants was low and the evaluation period was short; however, it provides crucial preliminary information to evaluate the effect of the beverage in a larger trial that would promote the use of the HS beverage during pregnancy to control hypertensive disorders of pregnancy and healthy biomarkers.

List Of Abbreviations: HS: Hibiscus sabdariffa L, BMI: Body Mass Index, WHO: World Health Organization, NCT: Number of Clinical Trial.

Competing Interests: The authors have no financial interests or conflicts of interest.

Author's Contributions: A-R,V.E., O-D, P., S-P, J. Designed the research. A-R,V.E. Wrote the original draft of the manuscript. P-D, R., G-T, J. conducted the experiments and collected the data. A-R, V.E., G-V, E. participated in the recruitment of the participants. O-D, P., S-P, J. supervised the project and acquired the funding. All authors read and approved the final version of the manuscript

Acknowledgements: We thank the MEDOMAI Clinic (Cuernavaca, Morelos, Mexico) for allowing the use of their facilities to recruit participant and the Secretaría de Ciencia, Humanidades, Tecnología e Innovación for the doctoral scholarship.

Funding: The study was supported by Secretaría de Investigación y Posgrado del Instituto Politécnico Nacional and the Universitat Autònoma de Barcelona.

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