IJPSR (2025), Volume 16, Issue 7 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 01 June 2025; received in revised form, 25 June 2025; accepted, 27 June 2025; published 01 July 2025

PREVENTIVE EFFECTS OF *HIBISCUS SABDARIFFA* LINN. (WHITE VARIETY) AQUEOUS EXTRACTS ON GLUCOSE AND LIPID METABOLIC DISORDERS CHARACTERISTIC OF PREDIABETES IN HIGH-CALORIE DIET-INDUCED WISTAR RATS

Jean-Michel Kouassi AKPO [1], Maxime Machioud SANGARE-OUMAR [*1], Félix Fanou GUINNIN [1] and Gisèle HOUEDJISSI [1, 2]

University of Abomey-Calavi (UAC) [1], Department of Animal Physiology, Laboratory of Physiology and Experimental Pharmacology, 06 BP 2584 Cotonou, Benin.
Laboratory of Research in Aquaculture and Aquatic Ecotoxicology [2], FSA, Parakou, Benin.

Keywords:

Type 2 diabetes prevention, *Hibiscus sabdariffa* L., High-calorie diet, Glucose and lipid metabolism

Correspondence to Author:
Maxime Machioud SANGARE-OUMAR

Senior Lecturer accredited by CAMES PhD in Physiology and Pharmacology, Lecturer and Researcher at the Faculty of Science and Technology, University of Abomey-Calavi03 BP 3481 Cotonou.

E-mail: sangoumarfr@yahoo.fr

ABSTRACT: Prediabetes, a transitional metabolic state preceding type 2 diabetes, is characterized by insulin resistance, moderate hyperglycaemia, dyslipidaemia, and oxidative stress. This study evaluates the preventive effects of aqueous extracts from the leaves, calyces, and seeds of *Hibiscus sabdariffa* L. (white variety) on glucose and lipid metabolism disorders induced by a high-calorie diet in Wistar rats. Eight groups of six male Wistar rats were fed for 12 weeks with either a standard diet, a high-calorie diet, or a high-calorie diet combined with two doses (100 or 200 mg/kg) of the plant extracts. The leaf and calyx extracts significantly reduced weight gain, BMI, blood glucose, insulin levels, HOMA-IR, and HOMA-B indices ($p < 0,05$), showing no significant differences compared to the standard diet group ($p > 0,05$). Postprandial blood glucose levels also approached those of the standard group. These extracts significantly lowered triglycerides, total cholesterol, and atherogenic indices (TG/HDL-C, CRI, AIP) ($p < 0.05$), while the reduction in HDL cholesterol remained non-significant ($p > 0,05$). In contrast, untreated high-calorie diet rats showed a significant decrease in HDL cholesterol ($p < 0,05$). The extracts also mitigated oxidative stress, with non-significant changes in SOD, catalase, and MDA levels ($p > 0.05$). Overall, *Hibiscus sabdariffa L*. leaf and calyx extracts exert a protective effect against early metabolic disturbances associated with type 2 diabetes, supporting their traditional use in Central and Northern Benin.

INTRODUCTION: Type 2 diabetes (T2D) is a chronic metabolic disease resulting from an imbalance between insulin production and utilization. It is usually preceded by a prediabetic state, characterized by insulin resistance, dyslipidemia, low-grade chronic inflammation, and oxidative stress [1].

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DOI: 10.13040/IJPSR.0975-8232.16(7).2097-15

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(7).2097-15

A high-calorie diet, rich in saturated fats, is one of the main factors involved in the onset of these early metabolic disorders [2]. However, conventional antidiabetic treatments can have notable side effects, especially gastrointestinal disturbances [3], which highlights the growing interest in effective natural alternatives.

Several studies have reported the antihyperglycemic and hypolipidemic properties of some medicinal plants [4–6], which may also play a beneficial role in preventing metabolic disorders induced by high-fat diets [7, 8]. Our previous investigations have shown that the white variety of *Hibiscus sabdariffa* L. is widely used in central and

northern Benin for the treatment of various ailments, including T2D. This study aims to evaluate the preventive effects of aqueous extracts from the leaves, calyces, and seeds of this plant on glucose and lipid metabolism alterations, as well as oxidative stress markers, induced by a high-calorie diet in Wistar rats.

MATERIALS AND METHODS:

Preparation of Organ Extracts: Each organ was first shade-dried and then ground into powder. Subsequently, 100 g of the powdered form of each white organ of *Hibiscus sabdariffa* L. were macerated in 1 L of distilled water for 24 hours. The supernatant was then filtered and dried in an oven at 37°C to obtain the extracts.

Preparation of Experimental Diets: The standard diet used in this study consisted of "rabbit fattening" pellets supplied by Véto-Services SA (Cotonou, Benin). Nutritional analysis, conducted at the Animal Nutrition Laboratory of the Faculty of Agronomic Sciences (FSA, UAC/Benin), revealed that the pellets contained 65.72% carbohydrates, 18,86% protein, and 7,5% lipids, with an energy value of 3358,4 Kcal/kg. The high-fat diet (HFD) was prepared following the protocol recommended by [9]. The proportions of the ingredients were calculated using the "Formulation-Lapin 2" software. The final composition of the HFD was confirmed by analysis at the Animal Nutrition Laboratory of the FSA.

TABLE 1: PROPORTIONS OF INGREDIENTS USED IN PREPARATION OF HFD

Ingredients	Quantities (g/kg)	Quantities (kg) for 80 kg
Soybean oil (37 kJ/g)	235 = 8695	18.8 kg
Casein (Cowbell milk) (17-20 kJ/g)	265 = 4505	21.2 kg
Corn starch (16 kJ/g)	186 = 2976	29.76 kg
Sugarcane juice (3-4 kJ/g)	10 = 30	0.8 kg
Sucrose (17 kJ/g)	60 = 1020	4.8kg
Sugarcane bagasse (0-1 kJ/g)	30 = 15	2.4kg
Wheat bran (8-10 kJ/g)	30 = 270	2.4 kg
Vitamin/mineral premix	15	1.2kg
L-cystine	4,2	0.32 kg
Choline bitartrate	2.5	0.2 Kg
Fish meal (18-22 kJ/g)	50 = 1000	4 kg
Wheat flour (14-15 kJ/g)	30 = 435	2.4kg
Pork fat (37-39 kJ/g)	82,3 = 3127.4	6.58 Kg
Energy value (kcal/kg)	5275.54	

TABLE 2: COMPOSITION THE DIETS

Nutritional Elements	Standard Diet	HFD Diet
Crude Protein	18.86 %	13.3 %
Crude Fat	7.5 %	43.6 %
Carbohydrates	57.68 %	24.8 %
Minerals and Vitamins	8.15 %	8.9 %
Moisture	7.87 %	9.4 %
Gross Energy	3358.4 Kcal/Kg	5275.54 Kcal /Kg

The experiments were conducted at the Laboratory of Experimental Physiology and Pharmacology (University of Abomey-Calavi), which has an animal facility where animals are bred and maintained under controlled conditions. All procedures adhered to ethical principles of animal experimentation, aiming to minimize suffering and reduce the number of animals used.

The methodology, adapted from [10], was used to evaluate the potential anti-hyperglycemic effect of aqueous extracts of *Hibiscus sabdariffa* L. on Wistar rats subjected to an unbalanced diet high in fat and sugar. Forty-eight (48) Wistar rats, aged 8 to 12 weeks, were divided into eight groups of six animals each, as presented in **Table 3** below.

TABLE 3: ANIMAL GROUPS

Groups	Diet + Treatments
STD	Standard diet + distilled water (10 mL/kg body weight)
ENG	High-fat diet (HFD) + distilled water (10 mL/kg body weight)

C100	HFD + Aqueous Extract of *Hibiscus sabdariffa* L. Calyces (AEHSC) at 100 mg/kg body weight
F100	HFD + Aqueous Extract of *Hibiscus sabdariffa* L. Leaves (AEHSL) at 100 mg/kg body weight
G100	HFD + Aqueous Extract of *Hibiscus sabdariffa* L. Seeds (AEHSS) at 100 mg/kg body weight
C200	HFD + Aqueous Extract of *Hibiscus sabdariffa* L. Calyces (AEHSC) at 200 mg/kg body weight
F200	HFD + Aqueous Extract of *Hibiscus sabdariffa* L. Leaves (AEHSL) at 200 mg/kg body weight
G200	HFD + Aqueous Extract of *Hibiscus sabdariffa* L. Seeds (AEHSS) at 200 mg/kg body weight

Administration of Extracts: Extracts dissolved in distilled water were administered directly into the stomach by intragastric gavage daily at 9:00 AM for a duration of 12 weeks. Body weight and length were recorded at the end of each week throughout the study period.

Blood Sampling and Biochemical Assays: In accordance with ethical guidelines for animal experimentation, all animals were anesthetized with ether prior to blood collection to minimize pain and distress. Blood samples were subsequently collected via retro-orbital plexus puncture during the experiment and at its conclusion. Samples were drawn into dry tubes for analysis of metabolic and biochemical parameters. Sampling was performed at weeks (W) W0, W4, W8, and W12 to measure metabolic markers including blood glucose, triglycerides, and insulin. At week 12, additional assays included total cholesterol, HDL-cholesterol, blood urea nitrogen (BUN), creatinine, transaminases (AST and ALT), and alkaline phosphatase (ALP). Blood samples were centrifuged at 3000 rpm for 10 minutes at 4°C, and the resulting plasma was used for analyses. All biochemical assays were conducted at the Regional Laboratory for Health Safety Expertise and Analysis, IRGIB Africa University, Akpakpa, Cotonou.

Glucose Measurement: Glucose concentration was determined by methode of Trinder [11]. In this assay, glucose is oxidized by glucose oxidase (GOD) producing gluconic acid and hydrogen peroxide (H_2O_2). The H_2O_2 then reacts with 4-aminoantipyrine (PAP) and chlorophenol in the presence of peroxidase (POD) to form a red quinoneimine dye. Absorbance of the colored complex was measured at 500 nm and is proportional to glucose concentration.

Blood Urea Nitrogen (BUN): Serum urea was quantified enzymatically following [12], with optimizations by [13]. The concentration of urea corresponds to the absorbance variation measured at 340 nm.

Aspartate Aminotransferase (AST): AST activity was assessed using the method of [14] as optimized by [15]. Enzymatic activity was determined by the decrease in absorbance at 340 nm.

Alanine Aminotransferase (ALT): ALT levels were measured according to the method developed by [16], with further optimizations. Enzyme activity was monitored by the reduction in absorbance at 340 nm.

Alkaline Phosphatase (ALP): ALP activity was evaluated by the colorimetric method of [17]. The formation of a red-colored complex, proportional to enzymatic activity, was measured at 510 nm.

Creatinine: Creatinine concentration was measured using themethod of [18], without pretreatment, optimized via a two-point kinetic method. Absorbance was recorded at 490 nm.

Total Cholesterol (TC): Total cholesterol was measured enzymatically as described by [19]. The assay involves: Hydrolysis of cholesterol esters into free cholesterol and fatty acids. Oxidation of cholesterol to cholest-4-en-3-one with concomitant production of H_2O_2. Reaction of H_2O_2 with phenol and PAP, catalyzed by peroxidase (POD), forming a colored quinoneimine measured at 500 nm.

HDL Cholesterol (HDL-C): HDL cholesterol was quantified using a selective detergent-accelerated direct method without specimen pretreatment [20].

Phase 1: LDL, VLDL, and chylomicrons release free cholesterol which produces hydrogen peroxide through enzymatic reaction; H_2O_2 is degraded via POD and DSBmT without forming a colored product.

Phase 2: A specific detergent solubilizes HDL cholesterol. The combined action of cholesterol oxidase (CO) and cholesterol esterase (CE) along with POD and 4-AAP produces a color reaction proportional to HDL-C concentration, measured at 600 nm.

Triglycerides: Triglycerides were assayed following [21] combined with the [11] reaction. Enzymatic hydrolysis of triglycerides into glycerol and fatty acids is followed by phosphorylation and oxidation of glycerol, generating H_2O_2. This reacts with 4-AAP and phenol in presence of POD to form a colored complex measured at 500 nm.

Insulin: Serum insulin was measured using a commercial REALY TECH kit (China) by chemiluminescent immunoassay (CLIA). The assay is based on antigen-antibody complex formation and detection of a light signal proportional to insulin concentration via luminometry [22].

Superoxide Dismutase (SOD): SOD activity was assessed by its ability to inhibit the reduction of nitroblue tetrazolium (NBT) by superoxide radicals generated *in-vitro* [23]. Enzymatic activity correlates with the decrease in absorbance at 560 nm.

Catalase (CAT): Catalase activity was measured using a colorimetric method assessing the decomposition of hydrogen peroxide (H_2O_2) into water and oxygen [24]. Blood samples incubated with H_2O_2 had residual peroxide quantified by a color reaction at 520 nm. Color intensity inversely correlates with catalase activity.

Malondialdehyde (MDA): Lipid peroxidation was evaluated by the thiobarbituric acid reactive substances (TBARS) assay [25]. Blood samples were treated with reagents, heated at 100°C for 60 min, then centrifuged. Absorbance of the supernatant was measured at 532, 450, and 600 nm. MDA concentration was calculated from absorbance differentials as an index of oxidative stress.

Oral Glucose Tolerance Test (OGTT): After 12 weeks of treatment and dietary intervention (standard or high-fat diet), animals were fasted for 12 hours with free access to water [26]. A glucose solution (2 g/kg body weight) was administered orally via a gastro-esophageal tube (1 mL/kg). Blood glucose was measured at baseline (T0) and at 20, 40, 60, 90, and 120-minutes post-administration using a glucometer with test strips (Gluco Dr).

Statistical Analysis: The results are presented as means ± standard deviations. Differences between means were assessed using one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test, performed with GraphPad version 10 software. A p-value < 0,05 was considered statistically significant in all experiments.

RESULTS: Overall, a progressive weight gain was observed in all animal groups over the 12-weeks experimental period, although the rates of increase differed among groups **Table 4**. The highest weight gain was recorded in animals fed the HFD without any treatment, while the lowest weight gain was observed in animals maintained on the standard diet without treatment (STD group). Animals that received the aqueous extracts from the three organs of *Hibiscus sabdariffa L.* at both doses exhibited significantly lower weight gain compared to the untreated HFD group ($p < 0.05$). Among the treated groups, the animals that received the leaf extracts showed the lowest weight gain, whereas those treated with the seed extracts exhibited a faster weight gain, closer to that of the untreated HFD group. However, the differences in weight gain among the treated groups were not statistically significant ($p > 0.05$).

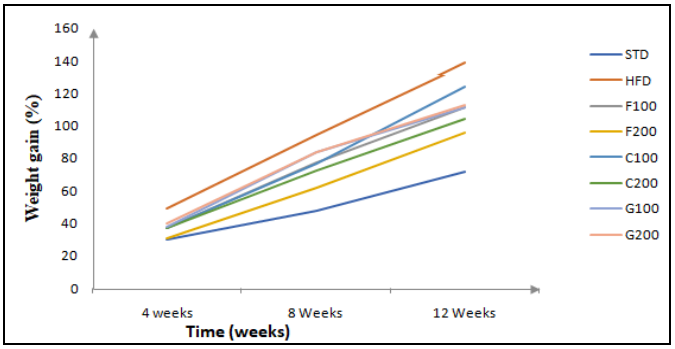

FIG. 1: VARIATION IN WEIGHT GAIN OVER TIME

Effect of *Hibiscus sabdariffa L.* (HS) Extracts on Body Mass Index (BMI): BMI increased in all groups throughout the experimental period, but at different rates (Table IV). After four weeks, HFD-fed animals treated with leaf or calyx extracts exhibited BMI values similar to those of the standard diet group ($p > 0.05$). In contrast, the BMI of HFD-fed animals treated with seed extracts, as well as that of the untreated HFD group, was significantly higher ($p < 0.05$). After 8 and 12 weeks, extracts from all three organs helped limit the increase in BMI, with a more pronounced effect observed for the leaf extracts. However, the BMI of treated animals remained significantly higher than that of animals fed the standard diet ($p < 0.05$).

TABLE 4: VARIATION IN BMI OVER EEK

	Week 0	Week 4	Week 8	Week 12
F100	0.31 ± 0.01	0.38 ± 0.01[a]	0.47 ± 0.02[b]	0.53 ± 0.02[b]
F200	0.31 ± 0.00	0.37 ± 0.00[a]	0.43 ± 0.01[a]	0.50 ± 0.01[b]
C100	0.31 ± 0.00	0.38 ± 0.00[a]	0.46 ± 0.01[b]	0.56 ± 0.00[b]
C200	0.32 ± 0.00	0.39 ± 0.00[a]	0.46 ± 0.01[b]	0.52 ± 0.01[b]
G100	0.33 ± 0.01	0.41 ± 0.01[b]	0.51 ± 0.01[c]	0.56 ± 0.01[b]
G200	0.32 ± 0.00	0.41 ± 0.01[b]	0.51 ± 0.01[c]	0.55 ± 0.01[b]
HFD	0.31 ± 0.00	0.42 ± 000[b]	0.52 ± 0.01[c]	0.61 ± 0.01[c]
STD	0.31 ± 0.00	0.38 ± 0.00[a]	0.41 ± 0.00[a]	0.45 ± 0.00[a]

Mean values obtained from 6 rats per group ± standard deviation. Values with the same letter are not significantly different ($p > 0.05$). Values with different letters are significantly different ($p < 0.05$).

Effect of HS Extracts on Liver and Kidney Mass: The administration of *Hibiscus sabdariffa* L. organ extracts, combined with a high-calorie diet, resulted in increased liver and kidney weights, with variations depending on the type of extract used **Table 5**. The liver weights of rats treated with both doses of leaf and calyx extracts did not significantly differ from those of the STD group ($p > 0.05$). In contrast, the percentage increases of 16.57%, 18.34%, and 26.16% observed in the G100, G200, and HFD groups, respectively, were significantly higher compared to the STD group ($p < 0.05$).Regarding the kidneys, animals treated with both doses of leaf and calyx extracts showed non-significant weight increases compared to the STD group. However, the kidney weights of animals treated with seed extracts at both doses, as well as those in the untreated HFD group, were significantly higher than those in the STD group ($p < 0.05$). Nonetheless, the increases observed in the G100 and G200 groups were significantly lower than those in the HFD group ($p < 0.05$).

TABLE 5: ORGAN MASS

Groups	F100	F200	C100	C200	G100	G200	HFD	STD
Liver	11.45	11.35±0.4	11.78 ±	11.51 ±	12.52 ±	12.71±	13.56	10.73 ±
% variation / STD	±0.27[a]	4[a]	0.27[a]	0.59[a]	0.21[b]	0.25[b]	±0.49[b]	0.31[a]
	+ 6.64	+ 5.67	+ 9,68	+ 7,23	+ 16,57	+ 18,34	+26.16	
Kidney	1.19 ±	1.17 ±	1.23±	1.21 ±	1.30 ±	1.36 ±	1.53 ±	1.11 ±0.1 [a]
% varation/ STD	0.02[a]	0.11[a]	0.06[a]	0,04[a]	0.04[b]	0.02[b]	0.04[c]	
	+ 5.00	+ 3.82	+ 8.53	+ 6.76	+ 15.29	+ 20.00	+ 35.01	

Mean values obtained from 6 rats per group ± standard deviation. Values sharing the same letter are not statistically different ($p > 0,05$). Values with different letters are statistically different ($p < 0,05$).

Carbohydrate Metabolism Parameters:

Effect of *Hibiscus sabdariffa* L. Extracts on Blood Glucose Levels: Over the 12-week experimental period (Week 0 to Week 12), blood glucose levels increased in all animal groups, but at varying rates **Table 6**. Between Week 0 and Week 4, significantly higher increases in blood glucose levels were observed in the G100 and HFD groups compared to the standard diet (STD) group ($p < 0.05$). In contrast, the increases observed in the other groups were not significantly different from those in the STD group ($p > 0.05$). By Week 12, the percentage increases in blood glucose levels in animals treated preventively with leaf (F100 and F200) and calyx (C100 and C200) extracts were not significantly different from those in the STD group ($p > 0.05$). However, significantly higher increases ($p < 0.001$) were recorded in the groups treated with seed extracts at both doses (100 and 200 mg/kg BW), as well as in the untreated HFD group. Comparisons between the two doses of each extract showed no significant differences within each plant part ($p > 0.05$). Notably, a decrease in blood glucose levels was observed between Week 8 and Week 12 in animals treated with both doses of the leaf and calyx extracts.

TABLE 6: EFFECT OF AQUEOUS EXTRACTS OF *HIBISCUS SABDARIFFA L.* ON BLOOD GLUCOSE LEVELS (MG/DL)

	Glucose Levels (mg/dL)								
	F100	F200	C100	C200	G100	G200	HFD	STD	P
Week 0	85.53 ± 3.74	87.40 ± 7.89	85.47 ± 5.61	84.83 ± 6.57	85.95 ± 7.29	87.35 ± 7,12	83.52 ± 5.33	85.52 ± 3.65	0.95

Week 4	89.93 ± 3.22[a]	88.4± 2.74[a]	90. 63± 2.81[a]	89.75 ± 2.52[a]	102.3 ± 6.97[b]	95.92 ± 2.7[b]	105.5 ± 8.28[b]	83.62 ± 1.29[a]	<0.0 001
% variation 0-4	+5.28± 5.73[a]	+1.9±11. 21[a]	+6.33± 5.85[a]	+6.37± 9.38[a]	+19.60±1 3.51[b]	+10.70±1 3.14[a]	+27.00± 15.18[b]	-2.10 ±3.53[a]	0.000 4
Week 8 %	96.17 ± 8.01[a]	93.19 ±5.01[a]	96.02 ± 8.76[a]	93.06 ± 4.39[a]	97.51 ± 6.97 [b]	100.8 ± 5.04[b]	99.48 ± 4.72[b]	86.62 ± 4.45[a]	<0.0 001
variation/ 0-8	+12.6±11.18[a]	+7.2±9.8 8[a]	+13.1±16 .75[a]	+10.3±11 .80[a]	+13.6±8. 94[b]	+16.3±14 .94[b]	+19.60±10 .37[b]	+1.41 ±6.27[a]	0.244 9
Week 12 %	90.95 ± 4.13[a] + 6.46	88.6±8.1 5[a]	91.67 ± 7.50[a]	90.42 ± 4.37[a]	103.8 ± 6.04[b]	102.3 ± 8.01[b]	124.3 ± 14.21[b]	86.10 ± 1.54[a]	<0.0 001
Variat 0-12	±7.54[a]	+2.40 ±13.76[a]	+ 7.73 ±12.52[a]	+ 7.20 ±11.18[a]	+ 20.86 ±7.12[b]	+ 17.55 ±6.71[b]	+ 49.24 ±18.68[c]	+ 0.83 ±4.67[a]	0.07

Mean values obtained from 6 rats per group ± standard deviation. Values sharing the same letter are not statistically different ($p > 0.05$). Values with different letters are statistically different ($p < 0.05$).

Effect of *Hibiscus sabdariffa L.* Extracts on Oral Glucose Tolerance (OGTT): During the oral glucose tolerance test (OGTT), blood glucose levels increased in all groups from time 0 to 40 minutes, followed by a gradual decrease between 60 and 120 minutes **Fig. 2.** In the untreated HFD group, the blood glucose spike was highly significant ($p < 0.001$) compared to the control group. In animals treated preventively with leaf and calyx extracts at 200 mg/kg BW, this elevation was attenuated, with blood glucose values not significantly different from those of the control group at all time points. At the lower dose (100 mg/kg BW), the same extracts induced significant increases ($p < 0.05$) in blood glucose levels. The seed extract, regardless of the dose, did not substantially attenuate the postprandial glucose elevation, showing glucose profiles very similar to those of the untreated HFD group.

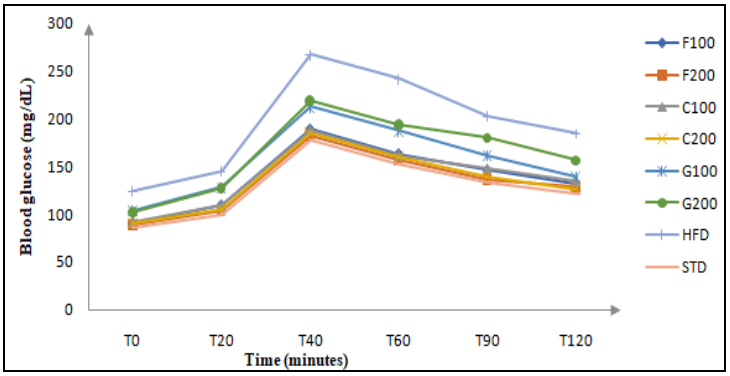

FIG. 2: ORAL GLUCOSE TOLERANCE TEST (OGTT) RESPONSE

Effect of *Hibiscus sabdariffa L.* Aqueous Extracts on Insulin level: Insulin levels increased in all animal groups throughout the experimental period (from Week 0 to Week 12) **Table 7**. Compared to the percentage increases recorded in animals fed a standard diet (STD group), the increases observed in animals preventively treated with the aqueous seed extracts (G100 and G200) and in the untreated HFD group were significant ($p < 0.05$). In contrast, the increases observed in animals preventively treated with the leaf and calyx extracts were not statistically significant. At Week 12, the percentage increases in insulin levels in the G100 and G200 groups were significantly lower than those observed in the HFD group ($p < 0.05$). For all three organ extracts (leaves, calyces, and seeds), the 100 mg/kg body weight doses did not produce significant differences when compared to the 200 mg/kg doses ($p > 0.05$) after 12 weeks of experimentation.

TABLE 7: CHANGES IN INSULIN LEVELS OVER TIME

	Insulin levels (µUI/mL)								
	F100	**F200**	**C100**	**C200**	**G100**	**G200**	**HFD**	**STD**	**P-value**
Week 0	12.39 ± 2.81	11.90 ± 2.67	11.24 ± 1.83	11.60 ± 2.53	12.22 ± 2.84	12.56 ± 2.9	11.22 ± 2.38	12.43 ± 2.13	0.9623

Week 4	13.76± 1.61 [a]	12.15±	13.92±	13.69±	24.62±	33.66±	28.66±	11.09±	<0.0001
%Variation	+16.5±32.45[a]	0.75[a]	0.79[a]	1.81[a]	0.76[b]	3.6[b]	4.07[c]	1.15[a]	
0-4		+6.89±	+26.4±2	+21.47±	+112.3±	+94.36±	+212.8±	-9.47±	<0.0001
		26.18[a]	0.04[a]	24.52[a]	59.54[b]	60.22[b]	78.78[b]	12.01[a]	
Week 8	20.30± 1.97[a]	18.06±	21.18±	19.52±	46.63±	49.20±	53.58 ±	13.68±	<0.0001
%Variation	+71.8±46.15[a]	1.98[a]	2.42 [a]	4,05[a]	8.25[b]	4.72[b]	9.1[b]	1.84[a]	
0-8		+55.9±2	+94.7±5	+71.9±3	+293.2±	+312.0±	+386.9±	+12.6±2	<0.0001
		6.92[a]	2.40[a]	6.21[a]	80.95[b]	115.0[b]	86.84[b]	5.07[a]	
Week 12	20.56±	18.56±	22.66±	20.58±	44.86±	41.28±	65.4 ±	15.21±	<0.0001
%Variation	1.79[a]	1.86[a]	1.40[a]	2.88[a]	5.52[b]	6.10[b]	3.69[c]	1,73[a]	<0,0001
0-12	+76.58±57.36[a]	+61.48	+88.98	+80.98±	+247.6	+246,5	+504.0±	+24.7	
		±32.85[a]	±37.96[a]	25.19[a]	±84.08[b]	±109,3[b]	124.6[c]	±21.51[a]	

Mean values obtained from 6 rats per group ± standard deviation. Values sharing the same letter are not statistically different (p > 0,05). Values with different letters are statistically different (p < 0,05).

Effect of *Hibiscus sabdariffa L.* Aqueous Extracts on Insulin Resistance (HOMA-IR): The insulin resistance values determined using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) were not statistically different at the beginning of the experiment (Week 0) ($p > 0.05$), as shown in **Fig. 3**. After four weeks (Week 4), the increases observed in the F100, F200, C100, C200, and G200 groups were not statistically significant compared to the STD group ($p > 0.05$). However, the HOMA-IR values in the G100 and HFD groups increased significantly relative to the STD group ($p < 0.05$).At both Week 8 and Week 12, HOMA-IR values in the G100, G200, and HFD groups remained significantly higher than those in the STD group ($p < 0.05$), while the values for the F100, F200, C100, and C200 groups were statistically comparable to those of the STD group ($p > 0.05$). Comparison of the two doses of each organ extract (100 mg/kg vs. 200 mg/kg body weight) showed no significant differences in HOMA-IR values ($p > 0.05$).

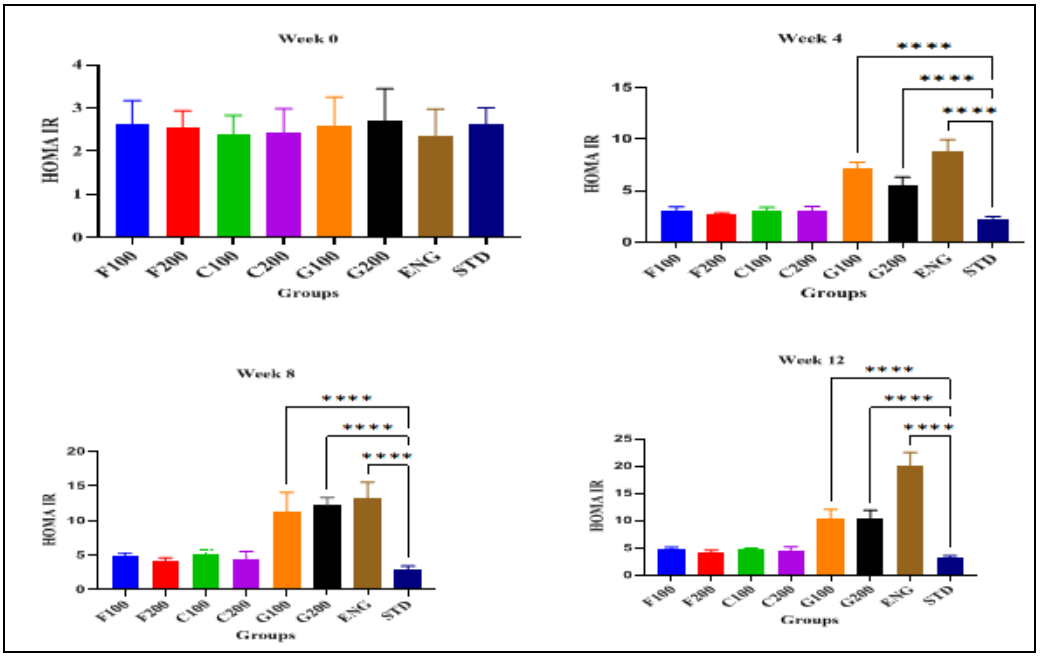

FIG. 3: VARIATION OF HOMA-IR ACROSS DIFFERENT GROUPS

Effect of *Hibiscus sabdariffa* L. Extracts on HOMA-β (Homeostasis Model Assessment of Pancreatic β-Cell Function): At the beginning of the experiment (Week 0), HOMA-β values (Homeostasis Model Assessment of Pancreatic β-Cell Function) were not statistically different across the groups ($p > 0.05$), as shown in the Week 0 graph of **Fig. 4.** After four weeks (Week 4), the HOMA-β values in the F100, F200, C100, C200, and G200 groups were not significantly different from those of the STD group. However, the HOMA-β values in the G100 and HFD groups increased significantly compared to the STD group ($p < 0.05$). At Week 8, HOMA-β values in the

G100, G200, and HFD groups were significantly higher than those in the STD group ($p < 0.05$). In contrast, HOMA-β values in the F100, F200, C100, and C200 groups remained statistically similar to those of the STD group. The same observations were made at Week 12, except that the HOMA-β value in the G100 group was no longer significantly higher than that of the STD group. Comparison of the effects of the two doses of each organ extract (100 mg/kg vs. 200 mg/kg body weight) showed no significant differences in HOMA-β values ($p > 0.05$).

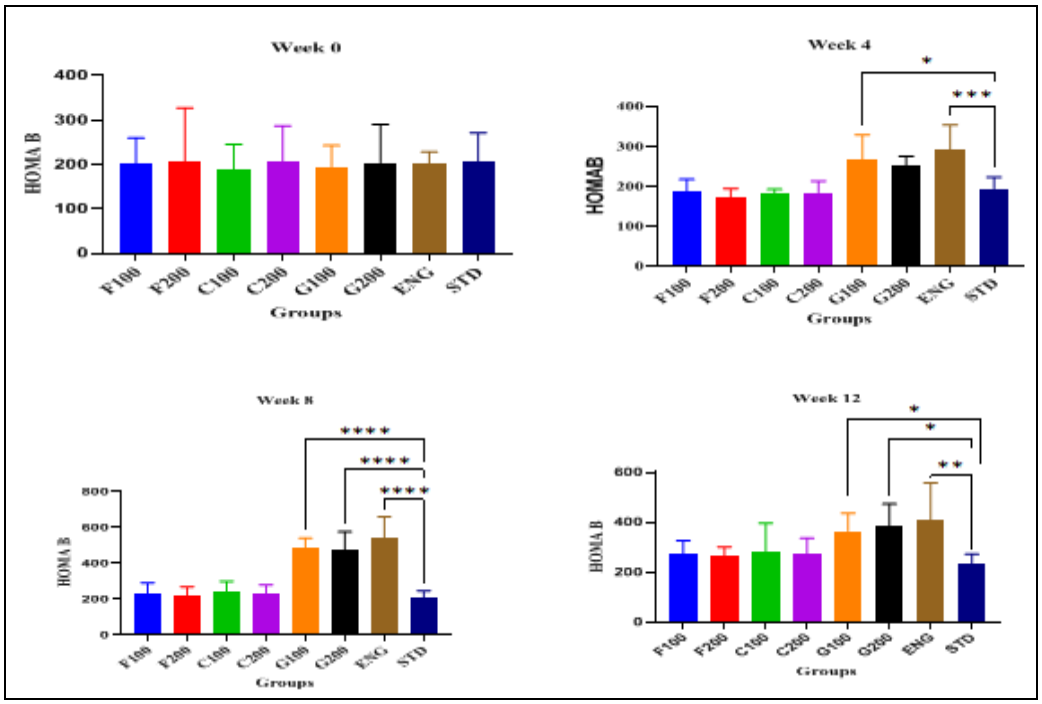

FIG. 4: VARIATION OF HOMA-β ACROSS DIFFERENT GROUPS

Effect of *Hibiscus sabdariffa L.* Extracts on the Insulin Disposition Index (DI): The Disposition Index (DI) assesses the ability of the pancreas to secrete insulin in compensation for insulin resistance. The DI values determined in this study are presented in **Fig. 5.**

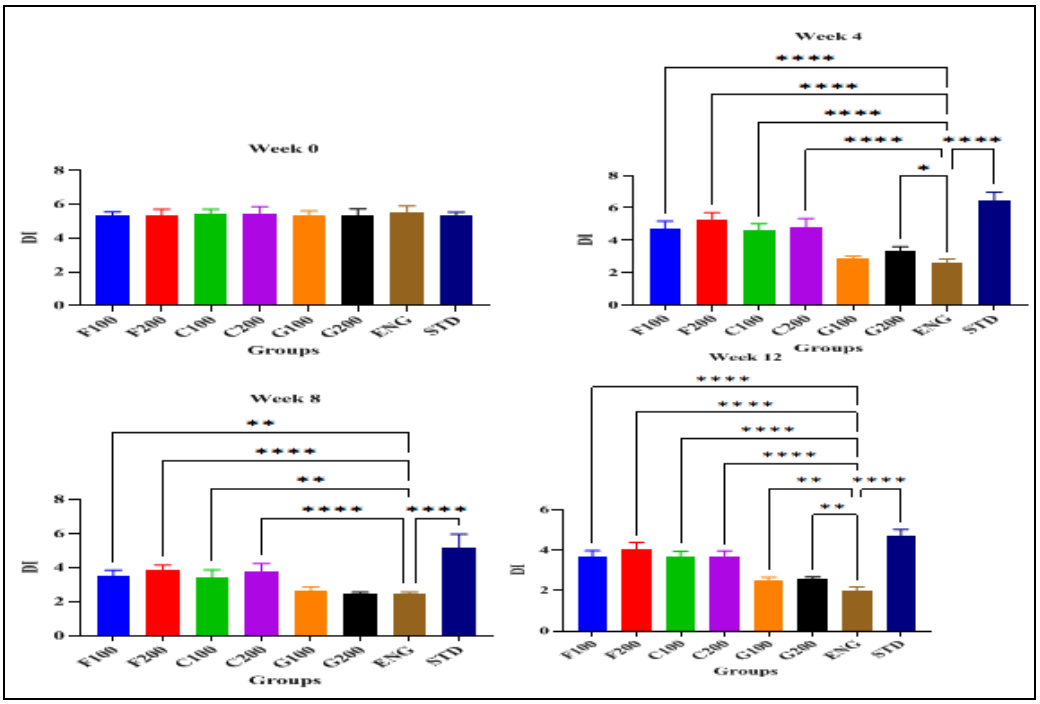

FIG. 5: VARIATION OF DI ACROSS DIFFERENT GROUPS

At baseline (Week 0), DI values did not differ significantly among the animal groups. From Week 4 to Week 12, DI values in the groups treated with *Hibiscus sabdariffa* L. extracts (F100, F200, C100, C200, G100, G200) and in the HFD group significantly decreased compared to the STD group ($p < 0.05$). When comparing the rates of decrease among the high-fat diet (HFD)-fed groups, significantly greater reductions were observed in the G100, G200, and HFD groups compared to the F100, F200, C100, and C200 groups ($p < 0.05$). The comparison between the two doses of each organ extract showed no significant differences in DI values between animals treated with 100 mg/kg body weight and those treated with 200 mg/kg body weight ($p > 0.05$).

Quicki (Quantitative Insulin Sensitivity Check Index): QUICKI is another parameter commonly used to assess insulin sensitivity. At the beginning of the experiment (Week 0), the QUICKI values did not differ significantly among the animal groups ($p > 0.05$), as shown in **Fig. 6**. At Week 0, statistically significant decreases of -16.66%, -12.12%, and -11.21% were observed in the HFD, G100, and G200 groups, respectively, compared to the STD group. In contrast, the decreases of -4.35%, -3.8%, -3.9%, and -2.1% observed in the C100, C200, F100, and F200 groups, respectively, were not statistically different from the STD group ($p > 0.05$).At Week 8, non-significant decreases of -4.78%, -5.55%, and -6.65% were observed in the F200, C200, and F100 groups, respectively, compared to the STD group ($p > 0.05$). However, significant decreases of -7.10%, -15.9%, -16.91%, and -17.52% were observed in the C100, G100, G200, and HFD groups, respectively ($p < 0.05$ vs. STD).At Week 12, non-significant decreases of -3.08%, -4.61%, -4.74%, and -4.91% were recorded in the F200, C200, F100, and C100 groups, respectively, compared to the STD group ($p > 0.05$). In contrast, significant decreases of -14.03%, -13.98%, and -20.28% were observed in the G100, G200, and HFD groups, respectively, when compared to the STD group ($p < 0.05$).

The comparison between the two doses of each *Hibiscus sabdariffa* L. organ extract revealed that the decreases observed in the F100, C100, and G100 groups were not significantly different from those observed in the F200, C200, and G200 groups, respectively ($p > 0.05$).

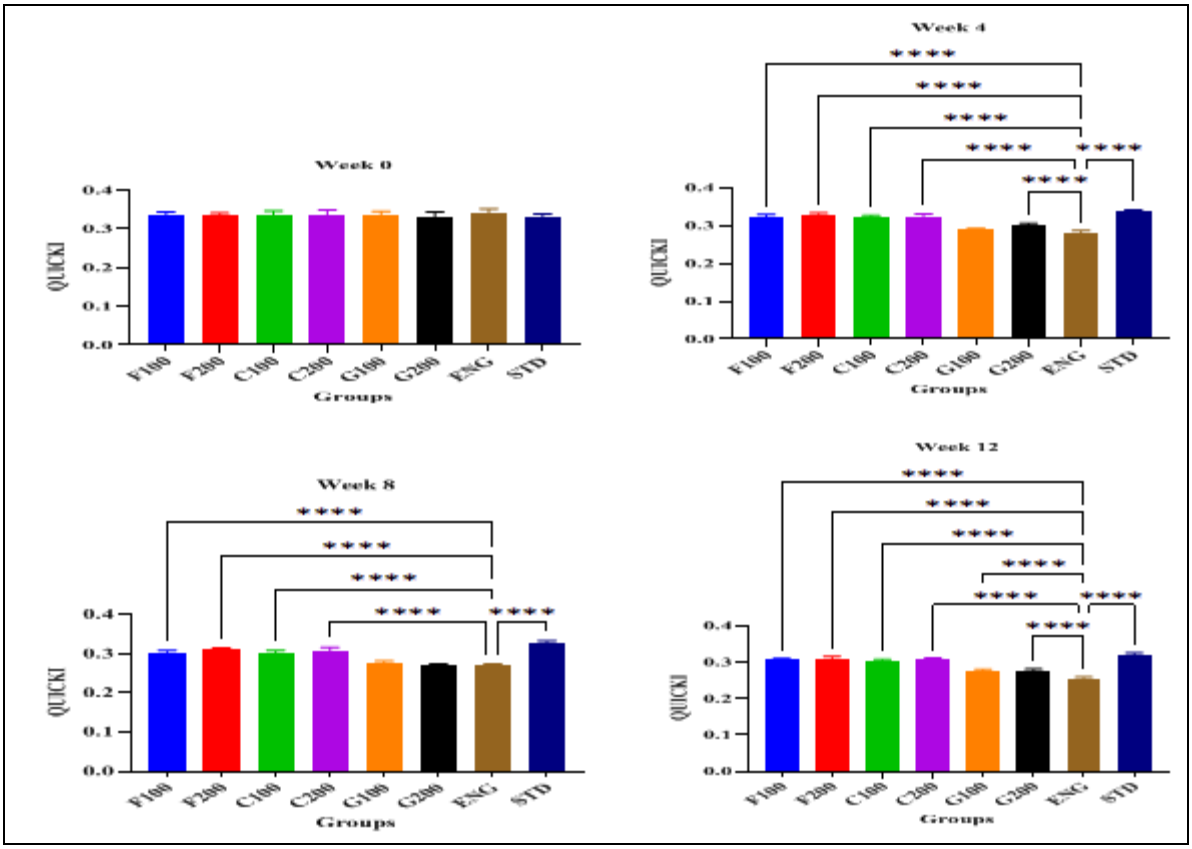

FIG. 6: VARIATION OF QUICKI OVER THE WEEKS

Effect of *Hibiscus sabdariffa* L. L. on Lipid Metabolism:

Effect of *Hibiscus sabdariffa L.* Extracts on Triglycerides: Compared to baseline values, triglyceride levels increased in all groups by the twelfth week (Week 12) of the experiment, with varying proportions across the different groups **Table 8**. After 4 weeks, only the HFD group exhibited a significantly higher increase compared to the STD group ($p < 0.05$). At both Weeks 8 and 12, significant increases in triglyceride levels were observed in the G100, G200, and HFD groups compared to the STD group ($p < 0.05$). In contrast, the increases observed in the F100, F200, C100, and C200 groups were not statistically significant when compared to the STD group. The comparison of the percentage increases between the two doses (100 mg/kg b.w. and 200 mg/kg b.w.) of each extract showed no statistically significant differences ($p > 0.05$). Furthermore, the increases in triglyceride levels in the groups treated with both doses of the extracts from the three *Hibiscus sabdariffa* L. organs were significantly lower than those observed in the HFD group.

TABLE 8: VARIATION IN TRIGLYCERIDE LEVELS OVER TIME

	Triglycerides en g/L								
	F100	**F200**	**C100**	**C200**	**G100**	**G200**	**HFD**	**STD**	**P**
Week 0	0.96 ± 0.26	0.85 ± 0.37	0.88 ± 0.29	0.93± 0.38	0.84 ± 0.37	0.88 ± 0.32	0.79 ± 0.38	0.98 ± 0.34	0.9642
Week 4	1.32 ±	1.01±	1.24 ±	1.14 ±	1.33 ±	1.40 ±	1.65 ±	1.03 ±	0.13
%Variation	0.43[a]	0.35[a]	0.38[a]	0.24[a]	0.38[a]	0.12[a]	0.26[b]	0.37[a]	
0-4	+49,55±76 ,44a	+34,33±7 5,80[a]	+60,84 ±93,68[a]	+38,90±5 8,47[a]	+60,91± 49,17[a]	+79,04±7 4,89[a]	+154.09 ±124.93[b]	+9.98± 13.07[a]	
Week 8	1.36 ±	1.09 ±	1.47 ±	1.23 ±	1.74 ±	1.64 ±	2.59 ±	1.12 ±	<0.000
%Variation	0.20[a]	0.32[a]	0.19[a]	0.32[a]	0.19[b]	0.16[b]	0.15[c]	0.40[a]	1
0-8	+47.74±28 .25[a]	+41.10 ±58.58[a]	+83.42 ±71.34[a]	+47.63 ±61.90[a]	+135.69 ±82.58[b]	+105.55 ±78.28[b]	+249.63 ±177.9[b]	+17.86 ±33.58[a]	
Week 12	1.47 ±	1.17 ±	1.49 ±	1,37 ±	1.81 ±	1.85 ±	2.36±	1.32	<0.000
%Variation	0.13[a]	0.11[a]	0.25[a]	0,10[a]	0.24[b]	0.14[b]	0.35[b]	0.31[a]	1
0-12	+62.19 ±40.47[a]	+53.89 ±48.40[a]	+79.73 ±38.82[a]	+65,52 ±54.71[a]	+155.21 ±118.76[b]	+129.62 ±69.63[b]	+251.24 ±143.57[b]	+43.69 ±42.47[a]	

Mean values obtained from 6 rats per group ± standard deviation. Values sharing the same letter are not statistically different ($p > 0,05$). Values with different letters are statistically different ($p < 0,05$).

Effect of *Hibiscus sabdariffa L.* Extracts on HDL Cholesterol (HDL-C): HDL-C levels decreased in all groups over the 12-week period, with varying degrees of reduction **Table 9.** After 4 weeks, significantly greater decreases were observed in the groups treated with calyx extracts (C100 and C200), seed extracts (G100 and G200), and in the HFD group compared to the STD group. However, in the groups treated with leaf extracts (F100 and F200), the reductions were not statistically significant compared to the STD group. From Week 8 to Week 12, significant decreases in HDL-C levels compared to the STD group were recorded in the F100, C100, G100, G200, and HFD groups, whereas the decreases observed in the F200 and C200 groups were not statistically significant ($p > 0.05$). The reductions observed with the 100 mg/kg b.w. dose of the leaf and calyx extracts (F100 and C100) were significantly greater than those observed with the 200 mg/kg b.w. dose ($p < 0.05$). For the seed extracts, the differences in HDL-C reduction between the two doses were not significant ($p > 0.05$) when compared to the HFD group.

TABLE 9: VARIATION IN HDL CHOLESTEROL L LEVELS OVER TIME

	HDL Cholesterol (g/L)								
	F100	**F200**	**C100**	**C200**	**G100**	**G200**	**HFD**	**STD**	**P**
W0	0.56 ± 0.08	0.53 ± 0.06	0.56± 0.01	0.59± 0.04	0.55 ± 0.11	0.59 ± 0.0	0.61 ± 0.07	0 .57 ± 0.06	0.5175
W4	0,42 ±	0,48±	0,32 ±	0,35 ±	0.30 ±	0.35 ±	0.29 ±	0.53 ±	<0.0001
%Variation	0,03a	0,02a	0.09b	0,14b	0.07b	0.04b	0,06b	0.03a	
0-4	-4.08± 14.02[a]	-7.73± 13 .50[a]	-41.59± 17.19[b]	-2.39± 20.76[b]	-3.35± 20.64[b]	-0.10± 8.50[b]	-2.52± 8.89[b]	-6,35± 13,74[a]	
W8	0.41[b]	0.51 ±	0,40 ±	0,46 ±	0,21 ±	0,23 ±	0,20 ±	0,54 ±	<0.0001

	0.02	0.03[a]	0,05[b]	0,03[b]	0.02[b]	0.05[b]	0.01[b]	0,02[a]	
%Variation	-5.10±	-2.10±	-28.13±	-1.16±	-8.91±	-9.78±	-6.81±	-4.31±	
0-8	14.18[b]	11.06[a]	11.14[b]	8.51[a]	12.81[c]	9.14[c]	4.73[c]	13.51[a]	
W12	0.37 ± 0.03[b]	0.46± 0.03[a]	0.25 ± 0.06[b]	0.46± 0.25[a]	0.20 ± 0.02[b]	0.23 ± 0.04[b]	0.18 ± 0.02[c]	0.51 ± 0.01[a]	<0.0001
%Variation	-2.34±	-1.56±	-54.16±	-1.62±	-2.38±	-0.68±	-9.42±	-0.17±	<0.0001
0-12	13.45[b]	7.91[a]	10.87[c]	7.94[a]	7.91[c]	7.44[c]	4.26[c]	10.17[a]	

Mean values obtained from 6 rats per group ± standard deviation. Values sharing the same letter are not statistically different (p > 0,05). Values with different letters are statistically different (p < 0,05).

Effect of Aqueous Extracts of *Hibiscus sabdariffa L.* on Total Cholesterol (T Cholesterol): Compared to baseline values, total cholesterol levels increased throughout the experiment, with varying degrees among the different groups **Table 10.**

At Week 4, the percentage increases observed in the groups of animals subjected to the HFD, whether treated or not, were not significantly different compared to the STD group. At Week 8, only the HFD group showed a significantly higher variation rate compared to the STD group ($p < 0.05$). At Week 12, the increases observed in the F100, F200, C100, and C200 groups compared to the STD group were not significant ($p > 0.05$), whereas those observed in the G100, G200, and HFD groups were significant ($p < 0.05$).

Comparison of the variations observed in these latter three groups showed that the increases in the G100 and G200 groups were significantly lower than those in the HFD group. The comparison of total cholesterol increases between the 100 mg/kg b.w. and 200 mg/kg b.w. doses for each extract indicated that these differences were not statistically significant ($p > 0.05$).

TABLE 10: VARIATION IN TOTAL CHOLESTEROL LEVELS

	Total Cholesterol (g/L)								
	F100	**F200**	**C100**	**C200**	**G100**	**G200**	**HFD**	**STD**	**P**
Week 0	0.86 ± 0,15	0.85 ± 0.15	0.83 ± 0.22	0.95 ± 0.22	0.87± 0.20	0.91 ± 0.37	0.93 ± 0.26	0.89 ± 0.14	0.9847
Week 4	1.20 ±	1.00 ±	1.24 ±	1.12 ±	1.12 ±	1.41 ±	1.32 ±	1.08 ±	<0.0001
%Variation	0.17[a]	0.11[a]	0.33[a]	0.12[a]	0.35a	0,17[a]	0.18[a]	0.004[a]	0.22
0-4	+40.60± 17.57	+20,93± 26.30	+53.78± 38.97	+23.33± 32.32	+33.23± 54.07	+75.09± 59.63	+50.31± 36.58	+23.56± 26.10	
Week 8	1.28 ±	1.19 ±	1.29 ±	1.25 ±	1.26 ±	1.35 ±	1.53 ±	1.13 ±	<0.0001
%Variation	0.19[a]	0.20[a]	0.36[a]	0.23[a]	0.32[a]	0.003[a]	0.08[b]	0.11[a]	
0-8	+50.16± 22.18[a]	+43.64 ±39.75[a]	+61.11 ±43.67a	+39.38 ±52.08[a]	+48.04 ±42.42[a]	+59.43 ±44.67[a]	+80.44 ±68.55[b]	+28.85 ±15.30[a]	0.616
Week 12	1.47 ±	1.37 ±	1.49 ±	1.46 ±	1.81 ±	1.78 ±	2.75 ±	1.20 ±	<0.0001
%Variation	0.13[a]	0.16[a]	0.25[a]	0.04[a]	0.24[b]	0.18[b]	0.11[c]	0.24[a]	0.0019
0-12	+75.89 ±38.21[a]	+66.20 ±44.26[a]	+89.51 ±49.57[a]	+62,12 ±49,24[a]	+114.7 ±43.47[b]	+127.3 ±101.5[b]	+227.7 ±139.0[b]	+38.58 ±32.93[a]	

Mean values obtained from 6 rats per group ± standard deviation. Values sharing the same letter are not statistically different (p > 0,05). Values with different letters are statistically different (p < 0,05).

Effect of *Hibiscus sabdariffa L.* Aqueous Extracts on the TG/HDL-C Ratio: The TG/HDL-C ratio is a recognized indicator of cardiovascular risk. It provides insights into insulin resistance and the quality of circulating lipids. At Week 0, TG/HDL-C values recorded in all animal groups were within the normal range (< 2) and were statistically equivalent to those of the STD group **Fig. 7.** At Week 4, significant increases compared to the STD group were observed in the HFD and G100 groups ($p < 0.05$), whereas the increases observed in the F100, F200, C100, C200, and G200 groups were not significant ($p > 0.05$). At Weeks 8 and 12, significant increases in the TG/HDL-C ratio were observed in the C100, G100, G200, and HFD groups compared to the STD group ($p < 0.05$). In contrast, the increases in the F100, F200, and C200 groups were not significant ($p > 0.05$).

The increase observed with the 100 mg/kg b.w. dose of the calyx extracts was significantly higher than that observed with the 200 mg/kg b.w. dose.

For the leaf and seed extracts, the increases recorded at both doses were not significantly different. When comparing the two doses, a significant increase in the TG/HDL-C ratio was observed in the C100 group compared to the C200 group, while the increases observed with the leaf and seed extracts were not significant.

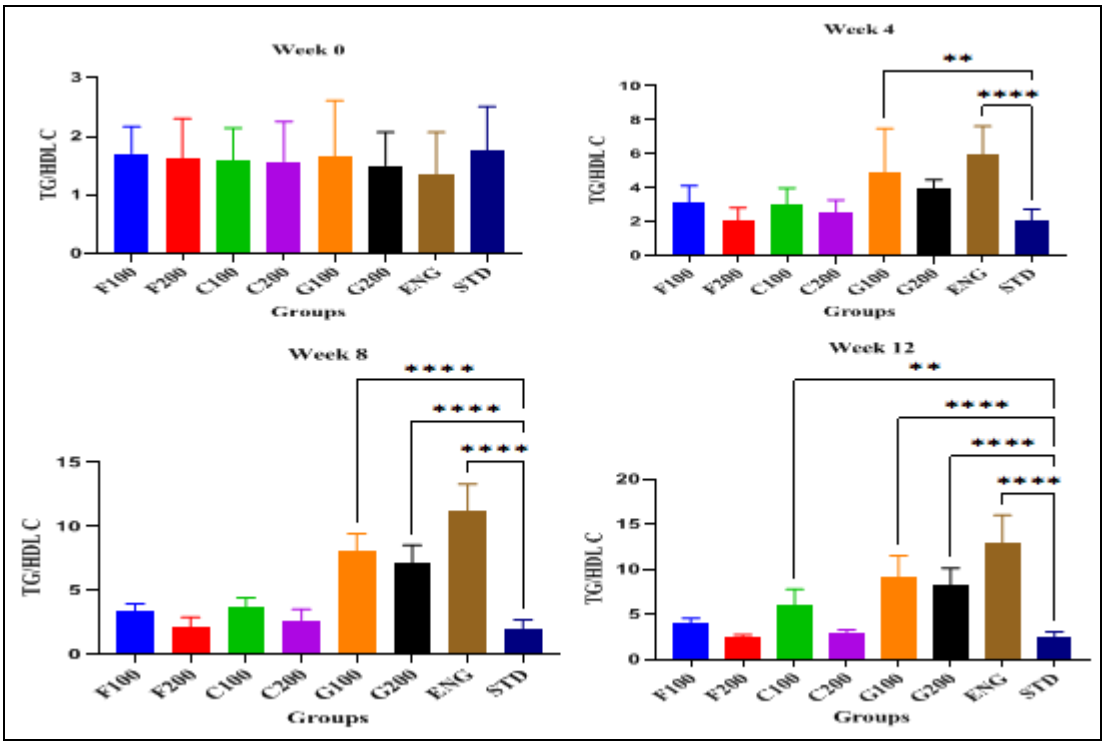

FIG. 7: VARIATION OF THE ATHEROGENIC INDEX OVER THE 12-WEEKS PERIOD

Effect of Aqueous *Hibiscus sabdariffa L.* Extracts on the Plasma Atherogenic Index (AIP): Compared to baseline values, the Atherogenic Index of Plasma (AIP) of the different groups increased over the 12-week experimental period **Fig. 8.**

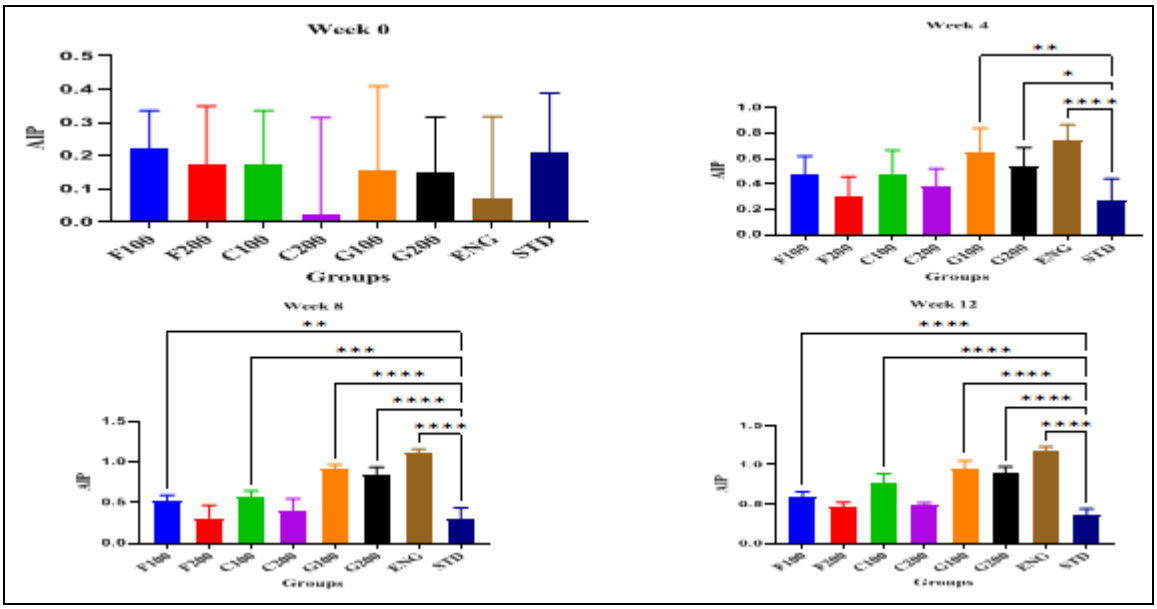

FIG. 8: VARIATION OF THE ATHEROGENIC INDEX OF PLASMA (AIP) OVER THE 12-WEEK PERIOD

Compared to the STD group, the increases observed in the groups treated with both doses of the aqueous extracts from the leaves and calyces (F100, F200, C100, and C200) were not significant

(p > 0.05) at Week 4. However, the increases recorded in the groups treated with the aqueous seed extracts and in the HFD group were significant (p < 0.05). At Week 8, only the higher doses of the leaf and calyx extracts (F200 and C200) produced increases that were not significant compared to the STD group. In the other groups, significant increases (F100 and C100) and highly significant increases (G100, G200, and HFD) were observed. At Week 12, still compared to the STD group, only the F200 extract resulted in a non-significant increase.

Effect of Aqueous Extracts of *Hibiscus sabdariffa L.* on Castelli's Coronary Risk Index I (CRI = Total Cholesterol/HDL C Ratio): The values of the coronary risk index (CRI), expressed as the Total Cholesterol/HDL C ratio, increased in all groups **Fig. 9.** At weeks 0 (W0) and (W 4), the increases observed in the F100, F200, C100, and C200 groups were not significant compared to the STD group (p > 0,05). However, in the G100, G200, and HFD groups, highly significant increases were observed compared to the STD group (p < 0,05). At week 12 (W12), the increases observed in the F100, F200, and C200 groups were not significant compared to the STD group (p > 0,05). In contrast, in the C100, G100, G200, and HFD groups, highly significant increases were observed compared to the STD group (p < 0,05).

The comparison of the increases observed with the 100 mg/kg bw dose and those with the 200 mg/kg bw dose of each extract indicates that the differences were not significant (p > 0.05) for the leaf and seed extracts. However, a highly significant increase was observed between the C100 and C200 groups.

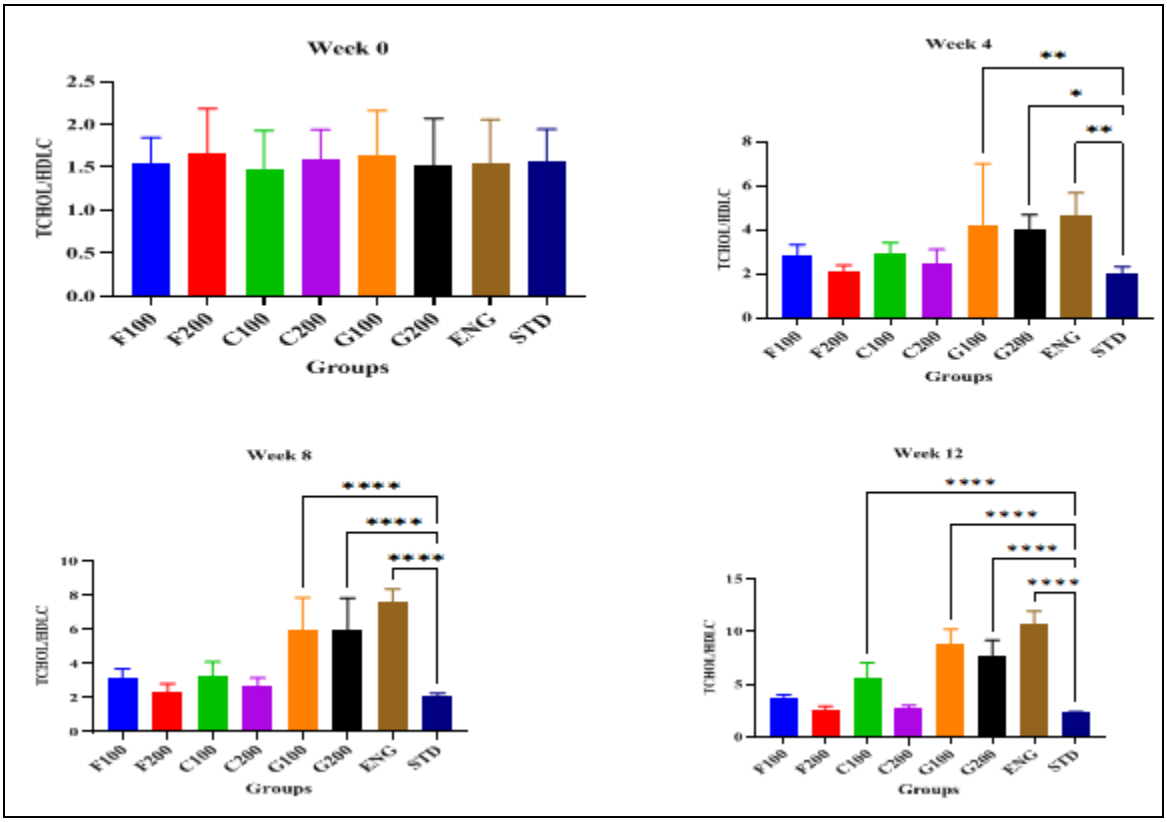

FIG. 9: VARIATION OF CASTELLI'S CORONARY RISK INDEX I OVER THE 12-WEEK PERIOD

Effect of *Hibiscus sabdariffa L.* Aqueous Extracts on Oxidative Stress Parameters: Plasma levels of superoxide dismutase (SOD) and catalase in animals fed a high-fat diet (HFD) without treatment, as well as those treated with seed extracts at both doses (G100 and G200), significantly decreased compared to the group fed a standard diet (STD) (p < 0.05), as shown in Table VII. In the groups of animals that received HFD along with leaf extracts (F100 and F200) or calyx extracts (C100 and C200), the observed decreases in these antioxidant parameters were not significant (p > 0.05). The decreases observed in the HFD group were significantly greater than those in the

groups treated with seed extracts (G100 and G200) ($p < 0.05$). Regarding malondialdehyde (MDA) levels, significant increases were observed in the HFD, G100, and G200 groups compared to the STD group ($p < 0.05$). However, in the groups treated with leaf extracts (F100 and F200) and calyx extracts (C100 and C200), the increases were not significant ($p > 0.05$).

TABLE 10: VARIATION OF SELECTED OXIDATIVE STRESS PARAMETERS

	F100	F200	C100	C200	G100	G200	HFD	STD
Anti. Oxydant	7.77	8.31±	7.83 ±	7.90 ±	6.45 ±	7.12±	4.61	8.87 ±
Enzymes	±0.20[a]	0.23[a]	0.76[a]	0.59[a]	0.76[b]	0.62[b]	±0.91[c]	1.14[a]
SOD (U/mL)	-12.44	-6.44	-11.79	-11.02	-27.39	- 19.82	-48.04	10.06
% Variation/STD	9.14±	9.77±	8.79±	9.63±	6.92±	7.77±	5.75±	1.10[a]
Catalase (U/mL)	0.71[a]	0,85[a]	0.57[a]	0.48[a]	1.19[b]	0.81[b]	0.72[c]	
% Variation/STD	-9,11	-2,89	-12.68	-4.29	-31.21	-22,78	-42.77	
Lipid	8.08 ±	7.83 ±	10,58±	8.53	13.01 ±	12.17 ±	15.12±	7.13
Peroxydation	0.38[a]	0.82[a]	0,56[a]	0.70[a]	0.41[b]	1.00[b]	0.74[b]	±0.47[a]
MDA (µmol/L)	+ 13.36	+ 9.88	+ 48.32	+16.62	+ 82.43	+70.58	+ 111.90	

Mean values obtained from 6 rats per group ± standard deviation. Values sharing the same letter are not statistically different ($p > 0,05$). Values with different letters are statistically different ($p < 0,05$).

Effect of Aqueous *Hibiscus sabdariffa L.* Extracts on Renal and Hepatic Parameters: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) are biomarkers that provide information about liver function. The results of serum measurements of these parameters are presented in **Table 11**. After 12 weeks of administration of aqueous *Hibiscus sabdariffa* (HS) extracts combined with a high-fat diet, compared to the STD group, an increase in ALT levels was observed in the G100, G200, and HFD groups, whereas a decrease was noted in the F100, F200, C100, and C200 groups. The increases observed in the G100 (4.08%) and G200 (6.12%) groups were not significant, while the increase in the HFD group (10.61%) was significant. The decreases observed in the F100 (-5.71%) and C100 (-4.08%) groups were not significant, whereas those in the C200 (-8.57%) and F200 (-11.83%) groups were significant. Regarding AST, the increases ranging from 8.17% to 16.89% compared to the STD group observed in the groups treated with the three plant extracts were not significant, whereas the increase in the HFD group (+24.80%) was significant ($p < 0.05$). As for urea, creatinine, and alkaline phosphatase (ALP) levels, the increases observed in the animals treated with both doses of the three HS organ extracts were not significant compared to the STD group ($p > 0.05$). However, in the untreated HFD group, the observed increases were significant ($p < 0.05$).

TABLE 11: EFFECT OF EXTRACTS ON RENAL AND HEPATIC FUNCTION ENZYMES

Groups	ALT (U/L)	AST (U/L)	Urea (mg/dL)	Creatinine (mg/dL)	ALP (U/L)
F100	38.5 ± 1.50[a]	73.83 ± 4,16[a]	28.83 ± 5.98[a]	0.73 ± 0.10[a]	109.1 ± 12.16[a]
F200	36 ± 2.53[b]	68.33 ± 4,80[a]	26.17 ± 4.66[a]	0.69 ± 0.05[a]	105.3 ± 5.05[a]
C100	39.17 ±1.50[a]	72.33 ± 4.80[a]	28.17 ± 4.21	0.721± 0.07[a]	104.8 ± 6.11[a]
C200	37.33 ± 2.16[b]	73.58 ± 12.79[a]	27.50 ± 3.67[a]	0.70 ± 0.12[a]	108.9 ± 6.38[a]
G100	42.50± 2.73[a]	73.58 ± 12.79[a]	28.83 ± 4.62[a]	0.73 ±0.12[a]	107.07 ± 4.10[a]
G200	43.33 ± 6.65[a]	73.67 ± 3.38[a]	28.17 ± 7.02[a]	0.76 ± 0.07[a]	109 ± 5.14[a]
HFD	45.17± 1.47[c]	78.83 ±8.23[b]	35.17 ±3.97[b]	0,85 ± 0.08[b]	123.2 ±5.67[b]
STD	40.83 ± 1,94[a]	63.17 ± 6,66[a]	26.33 ± 5.82[a]	0.65 ± 0.03[a]	103.3± 4.26[a]
P	<0.0001 (****)	0.01(*)	0.9472	0.4520	0.2300

Mean values obtained from 6 rats per group ± standard deviation. Values sharing the same letter are not statistically different ($p > 0,05$). Values with different letters are statistically different ($p < 0,05$).

DISCUSSION: All animals fed with the high-fat diet (HFD) experienced greater weight gain compared to those fed with the standard diet (STD), suggesting that our HFD promotes weight gain. Numerous studies have shown that fat-enriched foods lead to weight gain in rats [7, 27]. Oral administration of both doses (100 and 200 mg/kg body weight) of aqueous extracts from the three organs of the white variety of *Hibiscus sabdariffa* L. (HS) to HFD-fed Wistar rats demonstrated a potential anti-obesogenic effect. These rats exhibited a significant reduction in body weight

gain compared to untreated HFD-fed animals, suggesting that the plant may act on mechanisms regulating energy metabolism or lipogenesis. This potential anti-obesogenic effect of HS aqueous extracts is also suggested by their ability to partially limit the increase in body mass index (BMI) induced by the HFD. Although the BMIs of animals treated with the aqueous extracts remain significantly higher than those of the STD group, they are nonetheless significantly lower than those of the untreated HFD group. These results suggest a modulatory effect of HS aqueous extracts on weight gain, indicating a biological activity capable of attenuating, though not fully reversing, the deleterious metabolic effects associated with obesogenic diets. This partial efficacy profile could be attributed to an action on lipid and glucose metabolism pathways, satiety regulation, or to antioxidant or anti-inflammatory properties of certain bioactive compounds such as flavonoids, anthocyanins, leucoanthocyanins, tannins, and mucilages present in the plant [28].

Effect of *Hibiscus sabdariffa L.* Aqueous Extracts on Glucose Metabolism: The assessment of the anti-hyperglycemic effect of aqueous extracts from the leaves, calyces, and seeds of the white variety of HS reveals different profiles depending on the organ. The aqueous extracts of leaves and calyces administered with the HFD resulted in non-significant increases in blood glucose levels compared to the STD group. This suggests a relative capacity of these extracts to regulate blood glucose. This trend could be explained by the higher content of secondary metabolites, particularly flavonoids, in these two organs [28]. Indeed, metabolites such as flavonoids, mucilages, and tannins are known to not only slow intestinal glucose absorption but also to improve peripheral insulin sensitivity in skeletal muscles, liver, and adipocytes. Several studies have highlighted the protective effects of aqueous plant extracts against metabolic disorders and hyperglycemia associated with high-calorie diets [7, 29, 30].

Conversely, groups treated with aqueous seed extracts, like the untreated HFD group, showed significantly higher increases in blood glucose levels compared to the STD group, indicating a potential lack of efficacy at the doses used for this extract in mitigating metabolic disturbances induced by high-calorie food intake leading to hyperglycemia. Previous investigations have shown that the seeds of the plant contain fewer secondary metabolites and, for metabolites present in all three organs, the seed content was lower compared to leaves and calyces.

Administration of the HFD alone caused a significant increase in blood glucose accompanied by insulin hypersecretion in the HFD group compared to the STD group ($p < 0,05$). However, in animals that received both the HFD and aqueous extracts of HS leaves and calyces, this diet did not lead to an increase in either blood glucose or insulin secretion. This suggests that the plant extracts may act on blood glucose through extra-pancreatic mechanisms. Therefore, the white variety of HS may belong to plants exerting hypoglycemic effects independently of insulin action. The plant could act through mechanisms such as enhancing peripheral glucose uptake and/or inhibiting intestinal glucose absorption. Further studies measuring basal and postprandial blood glucose would be pertinent to determine whether the plant's effects on insulin levels are accompanied by improved glycemic control.

The significant increases in blood glucose and insulin levels in the groups fed the HFD and treated with seed aqueous extracts, though significantly lower than those of the untreated HFD group, may be linked to the lower potency of these extracts compared to those from other organs. This lack of potency could be related to the highly polar solvent used in this study (water) or to the differentiated metabolism of the organs. Since the seeds of the white variety of HS are rich in fats, such a solvent would only extract a fraction of their metabolites, unlike the other organs that contain little to no lipids. Seeds could potentially show similar activities to those of leaves and calyces if the extraction solvent had been an alcohol (ethanol or methanol).

By maintaining low blood glucose and insulin levels, the white variety of HS effectively preserves glucose homeostasis. This observation is supported by the stability of HOMA-IR and HOMA-B indices, which respectively assess insulin sensitivity and pancreatic beta-cell function and

have proven relevant in predicting type 2 diabetes risk [31]. For glucose homeostasis assessment, the disposition index (DI) and the QUICKI (Quantitative Insulin Sensitivity Check Index) were also used. The DI integrates insulin sensitivity and pancreatic response, while the QUICKI is based on fasting glucose and insulin concentrations, specifically reflecting peripheral insulin sensitivity. Aqueous extracts from the leaves and calyces of the white variety of HS significantly increased DI compared to the HFD group, suggesting relative protection of pancreatic cells from the stress associated with insulin hypersecretion in response to HFD-induced hyperglycemia. Similarly, the decreases in QUICKI observed in these groups were not statistically significant compared to the STD group, indicating that these extracts partially counteracted HFD-induced insulin resistance by improving peripheral insulin sensitivity [32, 33].

Evaluating glucose tolerance is essential for detecting early abnormalities in glucose metabolism, particularly in the context of a high-calorie diet. In our study, rats fed with the HFD exhibited marked increases in blood glucose at time points S2 and W4, followed by a gradual decrease that remained significantly higher than that of the control group. This profile is typical of insulin resistance and glucose intolerance, commonly observed in diet-induced obesity models [34]. Administration of leaf and calyx extracts at 200 mg/kg body weight mitigated this dysregulation, bringing the glucose curve back to levels comparable to those of the control animals. This normalization suggests a probable antidiabetic effect, either by improving insulin sensitivity, modulating intestinal glucose absorption, or stimulating peripheral glucose uptake [35]. Several studies have reported similar effects for extracts rich in polyphenols or flavonoids capable of positively modulating insulin signaling pathways, particularly via the PI3K/Akt pathway and GLUT4 expression [36]. However, the effect of the same extracts at 100 mg/kg body weight, although partially beneficial, was insufficient to restore normal glucose tolerance. This result supports the hypothesis of a dose-response relationship, often observed in pharmacodynamic evaluations of complex plant extracts (Sundaram *et al.*, 2018), and highlights the need for rigorous standardization and dosage optimization for any therapeutic development. In contrast, the seed extract did not show a corrective effect on the glucose curve, with increases observed at both early and late time points similar to those of the untreated HFD group. This lack of efficacy could be explained by the absence of active hypoglycemic compounds or their low bioavailability [37].

Effect of Aqueous Extracts of *Hibiscus sabdariffa L.* on Oxidative Stress: High-calorie foods cause the formation of reactive oxygen species (ROS). The accumulation of these in the body leads to several metabolic disorders, including inhibition of the PI3K/Akt pathway and activation of inhibitory kinases such as JNK and IKKβ, which contribute to insulin resistance and then type 2 diabetes [38]. To counteract the mechanisms behind these diseases, the body secretes antioxidant enzymes, notably superoxide dismutase (SOD) and catalase, which play a crucial protective role by neutralizing ROS and maintaining cellular redox balance favorable to insulin signaling [39, 40].

The aqueous extracts of the leaves and calyces of the white variety of HS caused non-significant decreases in serum SOD and catalase levels in the animal groups that received them compared to the STD group. This preservation of antioxidant activity is associated with a partial attenuation of insulin resistance, as evidenced by the QUICKI values and disposition index (DI) observed in these groups. These results could be linked to the antioxidant activity of the plant extracts.

Effect of *Hibiscus sabdariffa L.* Aqueous Extracts on Lipid Profile: In this study, extracts from the three organs of HS were administered preventively to Wistar rats on a high-fat diet (HFD) for 12 weeks. In the groups that received aqueous extracts of leaves and calyces, non-significant increases in triglycerides (TG) and total cholesterol (TC) accompanied by a non-significant decrease in HDL cholesterol (HDL-C) levels compared to the standard diet (STD) group ($p > 0,05$) were observed. In contrast, in the groups fed the HFD alone, TG and TC levels increased significantly, and HDL-C levels decreased significantly compared to the STD group ($p < 0,05$). These results suggest that the lipid imbalance induced by the HFD is partially attenuated by extracts from

these two plant organs. This effect likely results from bioactive compounds such as flavonoids [41], polyphenols [42], or saponins [43], known for their antioxidant and hypolipidemic properties. These findings agree with those of [44] and [7], who also demonstrated that plant extracts regulate lipid metabolism profiles in Wistar rats. The mechanisms of action of these compounds might involve promoting lipolysis and decreasing the expression of adipogenic and lipogenic genes.

Regarding the groups that received seed extracts, although the increases in TG and TC were significantly higher than in the normally fed group, these changes were also significantly lower than in the HFD-only group. This indicates that seed extracts less effectively attenuated lipid metabolic disorders induced by the HFD than leaf and calyx extracts. This could be explained by the relatively low potency of the doses of seed extracts used in this study or that the treatment duration was insufficient to achieve beneficial effects specifically for this organ. Indeed, several studies have shown the impact of dose and duration on lipid metabolism improvement by plant extracts[8,45]. A more detailed dose-response analysis would better assess the effects of these extracts on the lipid profile. Additionally, the TG/HDL-C ratio, atherogenic index TC/HDL-C, and the AIP (log TG/HDL-C), considered more sensitive indicators of cardiovascular risk than isolated lipid parameters [46], showed non-significant increases in treated groups compared to the standard control group. This indicates a partial reduction in cardiovascular risk and metabolic imbalances caused by the HFD in the untreated HFD group, where lipid disorders were significant.

This study also revealed a non-significant increase in malondialdehyde (MDA) in the serum of animals treated with both doses of leaf and calyx extracts of HS, unlike the HFD group where MDA increases were significantly high. This suggests that the extracts have antioxidant activity which, although insufficient to completely counter the increased lipid peroxidation induced by the HFD, limits it compared to the HFD group. These results align with [41] and [7], who showed that extracts from *Ziziphus lotus* (L.) Lam and HS calyces have beneficial effects on lipid metabolism and are cardioprotective.

Effect of White Variety HS Extracts and HFD on Hepatic and Renal Function Markers: Exposure to the high-fat diet (HFD) in animals that did not receive plant extracts led to a significant increase in hepatic (ALT, AST, and ALP) and renal (urea and creatinine) parameters compared to the group fed a standard diet (STD). These results confirm the ability of HFDs to induce hepato-renal alterations in animals [47, 48].

Conversely, in animals fed the same diet but who received preventive administration of extracts from the leaves, calyces, and seeds of *Hibiscus sabdariffa L.*, non-significant decreases in ALT levels were observed compared to the STD group. This suggests a potential protective effect of the plant on hepatic cells. However, non-significant increases were noted in the other markers of hepato-renal toxicity, namely AST, ALP, creatinine, and urea. These results may indicate a partial effect of the extracts in counteracting the harmful impacts of the HFD on these parameters.

The extracts from the leaves and calyces at the dose of 100 mg/kg body weight caused non-significant decreases in serum alanine aminotransferase (ALT), which is a sensitive marker of hepatic cell integrity, whereas the 200 mg/kg dose significantly reduced this parameter. This difference suggests a dose-dependent effect of these extracts, as higher concentrations of bioactive compounds may have a greater impact on this parameter compared to lower concentrations. The extracts from these two plant organs might act similarly to other medicinal plants that require minimal effective concentrations to interact with their endogenous targets (receptors, enzymes, etc.). It is possible that at a dose of 100 mg/kg body weight, the amount of available active compounds is too low to sufficiently counteract the effects of the HFD. In contrast, the 200 mg/kg dose likely increases bioavailability, promoting better reduction of the oxidative stress induced by the HFD and consequently preserving hepatocyte integrity, which leads to lower ALT production.

CONCLUSION: The results of this study suggest that the aqueous extracts of the leaves and calyces of the white variety of *Hibiscus sabdariffa L*. exert a notable preventive effect against the metabolic alterations induced by a high-fat diet in Wistar rats. These extracts helped limit disturbances in

carbohydrate and lipid metabolism, as well as oxidative stress markers, bringing the biological parameters closer to those observed in the healthy control group. These findings support the traditional uses of this plant in Benin and open promising perspectives for its integration into the prevention of prediabetes and associated metabolic disorders.

ACKNOWLEDGMENTS: The authors sincerely thank Dr ISSOTINA Zibrila Abdoulaye, Mr. BAMAI Conde Roland, Professor AHYI Virgileand all the staff of the Regional Laboratory for Sanitary Safety, Expertise, and Analysis at IRGIB Africa University (Akpakpa, Cotonou).

Funding: The authors declare that they did not receive any funding for this study.

Author Contributions: AKPO K. Jean-Michel: Concept and design of the study, or acquisition, analysis, and interpretation of data and drafting of manuscript. SANGARE-OUMAR Maxime Machioud: Drafting and critical revision of the manuscript for important intellectual content. GUINNIN Fanou Félix: Drafting and critical revision of the manuscript for important intellectual content. HOUEDJISSI Gisèle: Final approval of the version to be published

Data Availability: The data used in this study, including animal weights and measured biochemical parameters, are not publicly available. However, they may be provided by the corresponding author upon reasonable request and strictly for academic purposes.

CONFLICT OF INTEREST: The authors certify that there are no conflicts of interest.

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How to cite this article:
AKPO JK, SANGARE-OUMAR MM, GUINNIN FF and HOUEDJISSI G: Preventive effects of *Hibiscus sabdariffa* linn. (white variety) aqueous extracts on glucose and lipid metabolic disorders characteristic of prediabetes in high-calorie diet-induced wistar rats. Int J Pharm Sci & Res 2025; 16(7): 2097-15. doi: 10.13040/IJPSR.0975-8232.16(7).2097-15.

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