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Metabolic consequences of flavonoid and saponin extracts from *Gongronema Latifolium* leaves in offspring of rats that consumed sucrose during lactation

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ABSTRACT

Objectives: This study examines the metabolic consequences of saponin and flavonoid extracts of *Gongronema latifolium* leaves in rat offspring whose mothers consumed sucrose during breastfeeding.

Methods: Thirty-two female albino Wistar rats were randomly assigned to control group, given water only: sucrose group, given sucrose solution only; flavonoid groups, given sucrose solution and 100 mg/kg b.w. and 200 mg/kg b.w. of flavonoid and saponin groups, given sucrose solution and 100 mg/kg b.w. and 200 mg/kg b.w. of saponin extracts, for 3 weeks during lactation. Then the body, hepatic and pancreatic weights, food intake, glucose tolerance, lipid profile, insulin, and leptin levels of their offspring were measured.

Results: There was a significant decrease in the body weight (BW), food intake, and glucose level among the flavonoid and saponin groups compared to the control group. However, when compared to the sucrose group, there was a significant decrease in food intake, blood glucose level, triglyceride, and very low-density lipoprotein cholesterol levels and a significant increase in the BW. There was no significant difference in insulin and leptin levels, hepatic, and pancreatic weights among groups.

Conclusion: This study shows that *G. lactifolium* consumption among lactating rats maintains metabolic homeostatic as it protects against elevated blood glucose level and dyslipidemia in offspring post-weaning. It also suggests that the hypoglycemic and hypolipidemic properties of *G. latifolium* maybe as a result of saponin and flavonoids inherent in the plant.

Keywords: Cardiovascular disease, flavonoid, glucose level, *Gongronema latifolium*, hypoglycemic, hypolipidemic, lactation, metabolic syndrome, saponin

Introduction

The incidence of metabolic syndrome (MetS) has become an issue of global concern, as it is not a respecter of socioeconomic, race, country, or ethnicity; it is fueled by rapid urbanization, nutrition transition, and increasingly sedentary lifestyle.[1] Central obesity, insulin resistance, hypertension, fasting hyperglycemia, and dyslipidemia compute the spike in morbidity and mortality.[2,3]

Nutrition plays a pivotal role in shaping an individual's growth, organ development, body composition, and physiological function in the early developmental stage. Several experimental animal studies and clinical and epidemiological studies have shown that the nutrient a child is in contact with during the prenatal period and/or in early childhood is a crucial risk factor for obesity and MetS over their lifetime.[4] Studies have demonstrated the relationship between the consumption of sucrose by a mother during pregnancy and breastfeeding and the occurrence of insulin resistance, hypertension, obesity as well as other metabolic dysfunctions in the progenyin later life.[5,6] Furthermore, Katchy *et al*.,[7] reported the metabolic homeostatic role of *Gongronema latifolium* on rat off spring whose mothers consumed sucrose during breastfeeding as the extract prevented increased blood glucose level and dyslipidemia in offspring later in life.

In recent years, plant-based drugs are gaining momentum due to their potency in ameliorating certain health challenges and low toxicity.[8] The use of medicinal plants and nutrients in managing MetS is also gaining increasing attention and studies have reported the metabolic homeostasis, hypoglycemic, and hypolipidemic activities of certain plants including *G. latifolium*.[7,9-12] However, despite several reports on the

hypoglycemic, hypolipidemic, and metabolic homeostasis of crude extracts of *G. latifolium*, little has been reported on the effects of its bioactive phytochemicals. Therefore, this study examined the metabolic consequences of flavonoid and saponin extracts of *G. latifolium* on the rat offspring whose mothers consumed sucrose during breastfeeding.

Materials and Methods

Plant material

G. latifolium leaves were sourced locally, identified, and authenticated by the chief taxonomist of the Plant Science Unit of the Department of Biotechnology, University of Nigeria, Nsukka.

Preparation of flavonoid-rich and saponin-rich extracts

2,000 g of *G. latifolium* leaf was rinsed in water and dried under shade. It was then pulverized to a coarse powder using a Thomas-Wiley laboratory mill (model 4). Flavonoid-rich extract was prepared following the methods according to Arora and Itankar[13] with slight adjustments. Petroleum ether was used to defat 1 kg of the crude powder and 50% acetone for extraction using the cold maceration method. The extraction period was 3 days with fresh solvent replaced every 24 h. The resulting solution was again filtered into a volumetric flask. A rotary evaporator was used to dry the concentrate. The extract rich in saponin was prepared following the methods described by Harborne[14] with slight modifications. The dry leaves of *G. latifolium* were cut into little pieces. For 72 h, the dry herb thrice was thoroughly extracted with 80% MeOH, each extraction lasting 24 h. The filtered constituents were mixed and using rotavapor at 40°C its volume was reduced to 500 mL, hexane (4 × 250 mL) was used to defat the methanol extract, and afterward, the moisture was evaporated (rotavapor, 40°C).

Experimental animals and design

In this study, 32 female matured non-pregnant albino Wistar rats weighing 180–210 g were randomly assigned into ventilated metallic cages, with 12 h light and dark cycle at a temperature of 22°C and were provided standard commercial pelleted feed from vital feed, Nigeria Ltd. and water ad libitum. They were allowed 7 days to acclimatize before the experiment. At pro-estrous, the fertility of the male Wistar rats was confirmed before they were paired with the female rats in the ratio of 1:2 for proper mating. The 1st day that sperm was found in the vaginal smear of the female rats was considered day 1 of pregnancy.[15] The Wistar rats were given chow and water ad libitum throughout gestation. After delivery, the litters were culled eight pups per dam. The dams together with their pups, were randomly assigned to seven groups. Group 1 (control), dams were given water only; group 2 (sucrose group), dams were given sucrose solution (30% weight/volume) only; group 3, dams were given sucrose solution (30% weight/volume) and 100 mg/kg of flavonoid extract; group 4, dams were given sucrose solution (30% weight/volume) and 200 mg/kg of flavonoid extract; group 5, dams were given sucrose solution (30% weight/volume) and 100 mg/kg of saponin extract; group 6, dams were given sucrose solution (30% weight/volume) and 200 mg/kg of saponin extract; and group 7 (standard control), dams were given sucrose solution (30% weight/volume) and 5 mg/kg metformin. After the 3 weeks period of lactation, the pups were weaned on post-natal day (PND) 21. The off spring were then separated into different cages according to their groups and were giving unlimited access to food (chow) and water.

Measurement of food intake

Food intake was measured using a method by Katchy *et al*.,[7] and D'Alessandro *et al*.[5] The quantity of food administered to each animal (offspring) was weighed using a digital weighing scale and recorded daily from PND 22 to PND 42. Before the administration of the next meal, the leftovers were gathered and the quantity was recorded, then the value was subtracted from the original quantity that was administered the day before.

Chow consumed (g) = Quantity given (g) – Quantity leftover (g)

Body, hepatic, and pancreatic weight measurement

The body weights (BWs) of the pups were recorded weekly from PND 1 to PND 42 while the liver and pancreatic weights were measured on PND 42 using a digital weighing balance.

Oral glucose tolerance determination

The pups underwent an overnight (12 h) fast and 2 g/kg BW glucose solution was given orally on PND 42. Then blood was collected at 0, 30, 60, and 90 min intervals from the tail vein and one touch basic glucometer was used to determine the blood glucose levels in mg/dL.

Lipid profile and insulin level determination

The cardiac puncture method was used to get blood from the pups at PND 42 into specimen blood vessels; they were allowed time for clotting and centrifuged. The serum separation was used for insulin level and lipid profile determination. The determination of triglyceride and cholesterol levels was by glycerol phosphate oxidase method using Enzymatic Colorimetric Diagnostic Kits from Randox Laboratories, United Kingdom.[16] High-density lipoprotein cholesterol (HDL-C) was determined using the method according to Burstein *et al*.[17] Calculation of low-density lipoprotein cholesterol (LDL-C) is:

LDL-C (mg/dL) = TC - {HDL-C + TG/5},

VLDL-C (mg/dL) = TG/5

Where LDL-C is low-density lipoprotein cholesterol, TC is Total cholesterol, HDL-C is high-density lipoprotein cholesterol, and VLDL-C is very low-density lipoprotein cholesterol, TG: Tryglycerides.

An insulin enzyme-linked immunoassay (ELISA) kit was used to determine serum insulin level (uIU/mL).

Serum leptin measurement

After an overnight fast which lasted for 12 h, blood samples of the pups were collected into EDTA bottles from the tail vein on PND 42. They were allowed time for clotting and centrifuged. Serum leptin measurement (ng/mL) was done using a specialized leptin ELISA kit.

Data analysis

A one-way analysis of variance (ANOVA) was use to evaluate the difference of mean followed Student's Newman-Keuls *post hoc* test using IBM Statistical Package for the Social Sciences software version 20. The value of $P < 5\%$ (0.05) was considered statistically significant. The data are represented as mean ± standard error of the mean (SEM).

Ethical approval

Ethical approval for the study was obtained from the Research and Ethics Committee of the University of Nigeria Enugu Campus, Enugu, Nigeria with protocol number 085/09/2022.

Results

As shown in Table 1, maternal consumption of flavonoid and sapon in extracts of *G. latifolium* significantly decreased offspring BW when compared to control. However, the extracts significantly increased offspring BW when it was compared to the sucrose group and this competes favorably with the result of metformin on offspring BW.

As shown in Table 2, flavonoid and saponin extracts of *G. latifolium* showed no significant difference in the offspring's hepatic and pancreatic weights when it was compared to control and sucrose groups.

Table 3 shows the effect of maternal consumption of flavonoid and saponin extracts of *G. latifolium* during lactation on offspring's food intake post-weaning when it was compared with the control and sucrose groups from PND 22 to PND 42. The result revealed a significant reduction ($P < 0.05$) in offspring food intake when Flavonoid 100 mg/kg, saponin 100 mg/kg, and saponin 200 mg/kg were compared to normal control in the 4th, 5th, and 6th weeks. While Flavonoid 200 mg/kg significantly decreased BW in the 4th week but showed no significant difference in the 5th and 6th weeks. Furthermore, offspring food intake in flavonoid 100 mg/kg, saponin 100 mg/kg, and saponin 200 mg/kg groups revealed a significant reduction ($P < 0.05$) when it was compared to the sucrose group on the 6th week. However, animals treated with saponin 100 mg/kg showed the highest level of decrease in food intake.

As shown in Table 4, maternal consumption of flavonoid (100 mg/kg) and saponin (100 mg/kg and 200 mg/kg) extracts of *G. latifolium* significantly decreased blood glucose levels when it was compared to control and sucrose groups. However, the blood glucose of offspring treated with saponin 200 mg/kg showed the highest level of decrease.

As shown in Table 5, flavonoid and saponin extracts of *G. latifolium* had no significant effect on cholesterol, tryglycerides, HDL, LDL, and VLDL levels when they were compared to the control group. However, there was a significant decrease in triglyceride and VLDL levels when they were compared to the sucrose group.

As shown in Table 6, maternal consumption of flavonoid and saponin extracts of *G. latifolium* showed no significant difference in insulin levels when they were compared to control and sucrose groups. It also had no significant effect on leptin levels when they were compared to control. However, leptin levels of animals treated with saponin extract 100 mg/kg significantly increased when they were compared to the sucrose group.

Table 1: Effect of maternal consumption of flavonoid and saponin extracts of *Gongronema latifolium* on offspring body weight during lactation and post-weaning

Groups	Day 1 weight (g)	PND 7 weight (g)	PND 14 weight (g)	PND 21 weight (g)	PND 28 weight (g)	PND 35 weight (g)	PND 42 weight (g)
Normal control	6.17±0.48	15.97±0.0.44	23.00±1.40	34.20±2.73	51.83±0.81	70.03±4.37	103.43±12.96
Sucrose control	5.77±0.19	7.60±0.10*	13.30±0.17*	17.27±0.90*	27.37±0.62*	50.47±0.55*	72.60±2.25*
Flavonoid extract (100 mg/kg)	6.67±0.29	9.83±0.17*[a]	13.36±0.45*	14.57±3.74*	30.67±3.68*	58.07±3.91	80.83±2.34*
Flavonoid extract (200 mg/kg)	5.90±0.31	9.33±0.66*[a]	12.87±0.45*	16.77±0.56*	21.23±0.30*	54.37±7.12*	83.33±7.80*
Saponin extract (100 mg/kg)	6.67±0.15	10.87±0.78*[a]	22.20±0.14[a]	33.33±1.04[a]	54.03±0.30[a]	86.20±5.54*[a]	122.47±6.39[a]
Saponin extract (200 mg/kg)	5.47±0.29	9.97±0.41*[a]	18.57±0.64*[a]	29.07±0.52 [a]	49.83±0.71[a]	75.70±2.06[a]	86.77±2.99
Metformin (5 mg/kg)	6.13 ± 0.35	10.03 ± 0.33*[a]	12.80 ± 1.27*	18.60 ± 2.41*	26.47 ± 11.58*	59.47 ± 6.30	70.93 ± 3.30*

Each value represents mean±standard error of the mean. g: Gram, n=7, *P<0.05 versus normal control, [a]P<0.05 versus sucrose control. PND: Post-natal day

Discussion

MetS is a collection of metabolic dysregulations that includes insulin resistance, obesity, hypertension, and atherogenic dyslipidemia that occur together and it is linked with a heightened risk of developing diabetes and cardiovascular disease.[3] This study investigated the metabolic consequences of flavonoid and saponin extracts of *G. latifolium* leaves in the rat offspring whose mothers were fed sucrose during breastfeeding.

This study shows a decrease in BW of pups whose dams consumed sucrose during lactation compared to a control whose dams did not consume sucrose. Moreover, it is in agreement with the study of Katchy *et al*.,[18] and in disagreement with the studies of Toop *et al*.,[19] and Kendig *et al*.,[6] who showed that sucrose consumption during lactation had no effect on BW of the pups. The study also showed that flavonoid and saponin of *G. latifolium* L decreased offspring BW when compared to the control group and this agrees with reports of Katchy *et al*.,[7] and Amadi *et al*.[12] as well as confirms the reports of Nwaka *et al*.,[20] who noted that the reduction in BW of rats given *G. Latifolium* extracts could be a result of saponin inherent in the plant, as animals treated with saponin extract showed the highest decrease in BW. The decrease is assumed to be a result of adenosine monophosphate activation and protein kinase activation by *G. latifolium* saponins and polyphenols that are absorbable in the hepatic system, adipose tissues, and skeletal muscle which prompts a reduction in lipogenesis and gluconeogenesis, inhibits anabolism, mitochondrial biogenesis (catabolism), and increases lipolysis,[21,22] therefore leading to a reduction in BW. It also showed that flavonoid and saponin extracts of *G. latifolium* increased offspring BW when compared to the sucrose group and this corroborates previous reports that *G. latifolium* leave extract reverses rapid and significant weight loss which characterizes diabetes mellitus.[23,24]

Administration of flavonoid and saponin extracts of *G. latifolium* to lactating rats caused a decrease in food intake of the pups post-weaning and this indicates that components of the extract infiltrate the breast milk in the course of lactation to program decreased pups' food consumption.[12]

Flavonoid and saponin extracts of *G. latifolium* reduced blood glucose level when compared to control and sucrose groups

Table 2: Effect of maternal consumption of flavonoid and saponin extracts of *Gongronema latifolium* on offspring hepatic and pancreatic weights post-weaning

Groups	Liver weight (g)	Pancreatic weight (g)
Normal control	3.17±0.26	0.30±0.06
Sucrose control	2.87±0.24	0.27±0.03
Flavonoid extract (100 mg/kg)	4.10±0.76	0.30±0.06
Flavonoid extract (200 mg/kg)	2.93±0.26	0.40±0.00
Saponin extract (100 mg/kg)	3.17±0.03	0.30±0.06
Saponin extract (200 mg/kg)	3.80±0.12	0.37±0.03
Metformin (5 mg/kg)	3.53 ± 0.12	0.30 ± 0.06

Each value represents mean±standard error of the mean. n=7, P>0.05 for both hepatic and pancreatic weights

Table 3: Effect of maternal consumption of flavonoid and saponin extracts of *Gongronema latifolium* on offspring's food intake post-weaning

Groups	Weight (g) of food intake-week 4	Weight (g) of food intake-week 5	Weight (g) of food intake-week 6
Normal control	35.90±1.20	76.10±3.90	85.00±5.00
Sucrose control	20.01±1.50*	62.20±2.20	77.45±1.05
Flavonoid extract (100 mg/kg)	25.05±3.95*	53.50±3.50*	60.00±1.00*[a]
Flavonoid extract (200 mg/kg)	25.75±1.55*	65.00±5.00	69.70±0.30
Saponin extract (100 mg/kg)	16.50±2.90*	40.50±9.50*[a]	38.60±1.40*[a]
Saponin extract (200 mg/kg)	26.35±1.75*	46.50±6.10*	49.80±0.20*[a]
Metformin (5 mg/kg)	20.65 ± 2.55*	55.65 ± 9.35	52.85 ± 2.85*[a]

Each value represents mean±standard error of the mean, n=7,*=P<0.05 versus normal control, [a]=P < 0.05 versus sucrose control

Table 4: Effect of maternal consumption of flavonoid and saponin extracts of *Gongronema latifolium* on offspring oral glucose tolerance post-weaning

Groups	0 min (mg/dL)	30 mins (mg/dL)	60 mins (mg/dL)	90 mins (mg/dL)
Normal control	111.01±6.52	169.00±4.51	150.00±4.51	158.67±14.33
Sucrose control	111.67±9.53	145.67±14.67	150.00±9.29	134.33±8.37
Flavonoid extract (100 mg/kg)	98.67±7.36	132.33±7.06*	122.33±9.68*[a]	125.67±14.52*
Flavonoid extract (200 mg/kg)	101.67±11.68	160.33±17.03	156.33±11.57	140.67±7.97
Saponin extract (100 mg/kg)	75.00±6.43*[a]	130.67±2.33*	129.00±3.06	122.67±5.04*
Saponin extract (200 mg/kg)	68.00±3.01*[a]	115.67±6.49*[a]	111.00±5.03*[a]	103.33±7.06*[a]
Metformin (5 mg/kg)	69.33 ± 5.37*[a]	116.33 ± 2.03*[a]	115.33 ± 1.45*[a]	117.00 ± 4.93*[a]

Each value represents mean±standard error of the mean. n=7, *P<0.05 versus normal control, [a]P<0.05 versus sucrose control

Table 5: Effect of maternal consumption of flavonoid and saponin extracts of *Gongronema latifolium* on offspring lipid profile post-weaning

Groups	Cholesterol (mg/dL)	TG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)
Normal control	4.05±0.05	1.30±0.00	1.80±0.20	1.50±0.60	0.26±0.00
Sucrose control	5.10±0.70	1.55±0.05	1.35±0.25	2.45±0.45	0.31±0.01
Flavonoid (100 mg/kg)	4.95±1.15	1.20±0.00[a]	1.85±0.65	2.00±1.20	0.24±0.00[a]
Flavonoid (200 mg/kg)	4.55±0.65	1.50±0.20	1.80±0.90	1.75±1.25	0.30±0.40
Saponin (100 mg/kg)	4.05±0.05	1.20±0.10[a]	1.70±0.10	1.40±0.20	0.24±0.02[a]
Saponin (200 mg/kg)	4.10±0.00	1.40±0.10	1.d75±0.05	1.80±0.10	0.24±0.02[a]
Metformin (5 mg/kg)	4.25 ± 0.05	1.65 ± 0.05*	1.55 ± 0.15	1.90 ± 0.20	0.33 ± 0.01*

Where TG: Tryglycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein. Each value represents mean±standard error of the mean, n=7, *P<0.05 versus normal control, [a]P<0.05 versus sucrose control

Table 6: Effect of maternal consumption of flavonoid and saponin extracts of *Gongronema latifolium* on offspring insulin and leptin levels postweaning

Groups	Insulin (U/mL)	Leptin (ng/mL)
Normal control	14.91±2.05	1.91±0.02
Sucrose control	14.29±0.90	1.75±0.06
Flavonoid (100 mg/kg)	12.42±0.63	1.76±0.03
Flavonoid (200 mg/kg)	13.75±0.36	1.75±0.08
Saponin (100 mg/kg)	14.73±1.16	2.19±0.28[a]
Saponin (200 mg/kg)	13.67±0.45	1.78±0.09
Metformin (5 mg/kg)	13.22 ± 0.18	1.72 ± 0.10

Each value represents mean±standard error of the mean. n=7, *P<0.05 versus normal control, [a]P<0.05 versus sucrose control

and this suggests that the hypoglycemic and antidiabetic properties of crude extract of *G. latifolium* is due to the presence of flavonoid and mostly saponin inherent in the plant. Mechanisms through which flavonoid and saponin extract of *G. latifolium* lower hyperglycemia remains incompletely understood. The enzyme Glucokinase or Hexokinase D in the beta cells of the pancreas acts as the glucose sensor that determines insulin secretion threshold and in the hepatic parenchyma cells, it assists phosphorylation of glucose through hyperglycemia and as hexokinase D acts as a glucose sensor in hypothalamic neurons, with a vital role in the sympathomimetic reaction to increased blood sugar level. It shows that flavonoid and saponin act as catalysts and stimulators of the hexokinase D, to detect elevated level of sugar and concurrently phosphorylate the sugar to glucose-6-phosphate, which is an active step in blood glucose clearance and glycolysis.[25]

This study also showed that flavonoid and saponin extracts of *G. latifolium* decreased triglyceride, LDL, VLDL, and total cholesterol concentrations and increased HDL concentration when they were compared to sucrose group and the hypolipidemic activity of flavonoid and saponin of *G. latifolium* extracts may be due to the modification of the hydrophilic-hydrophobic interface betwixt the aqueous fraction of plasma and cholesterol by the extract in support of hypocholesterolemia and hypolipidemia.[25] However, the lipid profile was not affected by flavonoid and saponin extracts when they were compared to normal control.

The few potential limitations of this study are: first of all, even though Wistar rats are used in research due to practical and ethical reasons, metabolic responses in Wistar rats may not perfectly represent those in humans, thereby restricting the immediate applicability of the findings to human population; secondly, the consumption and metabolism of saponin and flavonoid may differ between rat pups, thereby affecting the observed metabolic consequences; thirdly, the study focused on specific metabolic indices, possibly neglecting important metabolic effects and markers such as hormone-sensitive lipase, skeletal muscle glycogen synthase, and lipoprotein lipase which may increase the risk of MetS; finally, despite the researchers' effectiveness, there may be unseen variables that influenced the outcome, leading to biased conclusions. To increase the accuracy and generalizability of the results, future research could address these limitations.

Conclusion

This study established that the metabolic homeostatic effect of flavonoid and saponin extracts of *G. latifolium* as the maternal consumption of the extracts during lactation protected against elevated blood glucose levels and dyslipidemia in offspring post-weaning and also suggested that the hypoglycemic and hypolipidemic effect of *G. latifolium* may be as a result of saponin and flavonoid inherent in the plant. Further research should explore more underlying mechanisms by which flavonoid and saponin extracts of *G. latifolium* elicited sugar-lowering effects and reverse dyslipidemia is warranted to fully harness the therapeutic potentials of *G. latifolium* in the management of obesity, diabetes, and MetS.

Authors' Declaration Statements

Ethical approval

Ethical approval for the study was obtained from the Research and Ethics Committee of the University of Nigeria Enugu Campus, Enugu, Nigeria with protocol number 085/09/2022.

Consent for publication

None

Availability of data and material

To be provided by the corresponding author on request.

Competing interests

In accordance with the standardized disclosure form recommended by the International Committee of Medical Journal Editors (IJMJE), each author hereby affirms the following: Funding and Support: The authors affirm that they did not receive any financial assistance or services from any organization for the research presented in this submission. Financial Associations: All authors assert that they do not currently have any financial affiliations or have had any financial interactions within the last 3 years with organizations that may have a vested interest in the research presented. Other Associations: The authors confirm that there are no other personal or professional relationships or activities that might be perceived as having an influence on the research submitted.

Funding statement

None

Authors' contributions

All authors contributed equally. The author CNO did the conceptualization and designed the study. Authors CNO, DCI, and OMO performed the methodology. Authors CNO, BUA, and AK did the formal analysis. Authors CNO, DCI, and OMO wrote the original draft. BUA supervised the study. All the authors contributed to drafting the work, critically revised the manuscript, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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