Evaluation of the Regulatory Effect of Ripe Fruit Juice of *Saba senegalensis* on Hyperglycemia in *Rattus norvegicus*

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ABSTRACT--- *The objective of this study is to evaluate the ability of Saba senegalensis ripe fruit juice to regulate orally induced hyperglycemia in Rattus norvegicus. To do this, trace elements were first searched for in the juice of ripe fruit of Saba senegalensis by the calcination-mineralization method. Then, amino acids and vitamins C and B were searched for by the HPLC method. Finally, the evaluation of the regulatory activity of Saba senegalensis juice was done by induction of orally induced hyperglycemia after the ingestion of 75 grams of glucose. The results of this study reveal that the juice of ripe fruit of Saba senegalensis contains trace elements such as calcium, phosphorus, magnesium, potassium, sodium, manganese, zinc, copper and iron with respective contents of 1.20 ± 0.03; 0.42 ± 0.08; 0.95 ± 0.07; 1.40 ± 0.09; 0.09 ± 0.005; 0.27 ± 0.03; 0.96 ± 0.06; 0.94 ± 0.07 and 1.41 ± 0.02 µg/g dry matter. It also contains vitamins C and B1 as well as amino acids such as cysteine, proline and leucine, of which the latter is an essential amino acid. It appears from this study that Saba senegalensis fruit juice contains trace elements, amino acids and vitamins. The presence of these elements in the juice of ripe fruit of Saba senegalensis helps to lower the hyperglycemia induced by the consumption of glucose and to normalize blood sugar levels.*

Keywords--- hyperglycemia, *Rattus norvegicus*, *Saba senegalensis*, juice

1. INTRODUCTION

The fruit of *Saba senegalensis* is a globular shell that contains seeds coated in orange-yellow pulp, very soft, juicy, a little sweet and tangy[1]. Green fruits, cooked with salt, are a diuretic[2] while ripe fruits are anorexic, antiscorbutic, stimulating, tonic, and help treat constipation[3]. Ripe fruit juice from *Saba senegalensis* can be consumed directly or as a juice diluted in water, to which sugar is added. This last form of consumption suggests that a good amount of sugar is ingested during the *Saba senegalensis* fruit season among these consumers. It is on this hypothesis that this study is conducted to evaluate the ability of *Saba senegalensis* fruit juice to regulate orally induced hyperglycemia in *Rattus norvegicus*. To achieve this, the following specific objectives have been set :

- dose some trace elements, amino acids and vitamins in the juice of ripe fruit of *Saba senegalensis*,
- induce hyperglycemia in *Rattus norvegicus* through the consumption of 75 grams of glucose per kilogram of body weight,
- evaluate the regulatory effect of ripe fruit juice of *Saba senegalensis* on induced hyperglycemia.

2. MATERIALS AND METHODS

2.1. Materials

The plant material consists of ripe fruits of *Saba senegalensis* (Figure 1) and rats of the species *Rattus norvegicus* (Figure 2).

Figure 1 : ripe *Saba Senegalensis* fruits

Figure 2 : *Rattus norvegicus*

2.2. Methods

2.2.1. Obtaining *Saba senegalensis* fruit juice

The ripe fruits of *Saba senegalensis* harvested in Korhogo – Côte d'Ivoire, were sent to the laboratory of the Peleforo GON COULIBALY University in Korhogo to extract the juice (Figure 3). Part of this juice was used to determine minerals, amino acids and vitamins, and to evaluate the ability of the juice of ripe fruit of *Saba senegalensis* to normalize blood sugar levels.

Figure 3 : ripe fruit juice of *Saba senegalensis*

2.2.2. Determination of trace elements

The calcination - mineralization method[4] was used to determine the mineral content of the juice of ripe fruit of *Saba senegalensis*. To do this, the ripe fruit juice of Saba senegalensis was first dehydrated for 24 hours in a Memmert-Germany oven at 60 °C. Then it was put in glass vials to be burned. An amount (0.4 g) of the dehydrated *Saba senegalensis* juice was weighed using a scale in a 30 mL porcelain crucible. This test socket was placed in a muffle furnace (Naberthem-Germany) set at 550 °C for 5 hours. After cooling, 2 mL of 0.5 N chloridryic acid was added to the ash obtained and brought to full evaporation in a sand bath. The final residue recovered is filtered through a 100 mL volumetric flask and distilled water has been added to reach the gauge line. Five (5) mL of the filtrate were taken for the determination of minerals (K, Fe, Zn, Mg, Cu) by the atomic absorption spectrophotometer (AAS 20 type VARIAN, Australia). The operation has been duplicated. The wavelengths at which potassium (K), iron (Fe), zinc (Zn), magnesium (Mg), and copper (Cu) were read were 766.5 nm; 248.3 nm; 258 nm; 285.2 nm and 324.7 nm respectively. The results of the optical densities of each mineral were used to determine the amounts (ppm) of minerals contained in the juice of *Saba senegalensis*. The mineral contents (T) were determined as follows :

$$T = [(C_{ess} - C_{bl})\ V] / P_{ess} \quad (I)$$

T : µg/g content
P_{ess} : test portion (g)
C_{ess} : sample concentration (mg/mL)
V : recovery volume of the test (mL)
C_{bl} : white concentration (mg/mL)

2.2.3. Amino acid determination

The determination of amino acids (cysteine, leucine, proline) in the juice of *Saba senegalensis* from methanol/water eluents (50 : 50) was done by HPLC. Ten (10) mg of the control of the amino acid of interest were weighed in a 20 mL vial and dissolved with 1N hydrochloric acid. One (01) gram of dehydrated *Saba senegalensis* juice was weighed in a 20 mL vial and dissolved with 1N hydrochloric acid. The two (02) prepared solutions were each transferred to the containers of the device dedicated to them. Then, the mobile phase was prepared from the methanol/water eluents (50 : 50) and transferred into the HPLC injection loop. This mobile phase has driven the solutes through the column. Afterwards, a high-pressure pump pushed the methanol/water eluents (50 : 50) into the chromatographic system at a flow rate of 1.2 mL/min. In addition, the autosampler injected the *Saba senegalensis* juice solution (sample) and the stationary phase column separated the compounds from the Saba senegalensis juice. Also, an analyte detector made it possible to search, detect and measure the chemical species of interest. Finally, a computer and a printer connected to the device generated and printed the chromatogram, respectively. The amino acid content (T) of *Saba senegalensis* juice was calculated as follows :

$$T\ (\%) = [(AE * MT) / (AT * ME)]\ 100 \quad (II)$$

AT : witness area
AE : test area
ME : mass of the test (g)
MT : mass of the witness (g)

2.2.4. Dosage of vitamins C and B

The determination of vitamins in *Saba senegalensis* juice from methanol/acetonitrile eluents (50 : 50) was done by HPLC. Ten (10) mg of the control of the desired vitamin were weighed in a 20 mL vial and dissolved with 1N hydrochloric acid. One (01) gram of dehydrated *Saba senegalensis* juice was weighed in a 20 mL vial and dissolved with 1N hydrochloric acid. The two (02) prepared solutions were each transferred to the containers of the device dedicated to them. Then, the mobile phase was prepared from the methanol/acetonitrile eluents (50 : 50) and transferred into the HPLC injection loop. This mobile phase has driven the solutes through the column. Afterwards, a high-pressure pump pushed the methanol/acetonitrile eluents (50 : 50) into the chromatographic system at a flow rate of 1.2 mL/min. In addition, the autosampler injected the Saba senegalensis juice solution (sample) and the stationary phase column separated the compounds from the *Saba senegalensis* juice. Also, an analyte detector made it possible to search, detect and measure the chemical species of interest. Finally, a computer and a printer connected to the device generated and printed the chromatogram, respectively. The vitamin (T) content of Saba senegalensis juice was calculated as follows :

$$T\ (\%) = \frac{AE * MT}{AT * ME} 100 \quad \text{(III)}$$

with

AT : witness area
AE : test area
ME : mass of the test (g)
MT : mass of the witness (g)

2.2.5. Evaluation of the regulating effect of Saba senegalensis juice on blood glucose

The assessment of the regulatory activity of Saba senegalensis juice was done by inducing orally induced hyperglycemia after ingestion of 75 grams of glucose[5]. Oral hyperglycemia (OGTT) is a way to see how the body reacts after ingesting glucose. To do this, blood sugar levels (blood glucose) are first measured on an empty stomach in rats, then blood sugar is measured for 1 hour; 2 and 3 hours after glucose consumption.

Experimental protocol

Thirty (30) rats weighing between 150.39 and 180.16 g ; 25-week-old children were first fasted for 12 hours. Then, they were divided into 5 homogeneous batches of 6 rats each, including three (03) males and three (03) females. After 12 hours of fasting, the tail end of each rat in each batch was lightly cut off with a sterile blade and the blood was deposited on the strip. The blood strip was inserted into the blood glucose meter and the value displayed by the blood glucose meter was the fasting rat's blood glucose at time zero (T0). After blood glucose measurement at time T0, rats were treated as follows [6] :

- batch 1 (negative control lot) did not receive glucose
- batch 2 (positive control) received glucose at a dose of 75 g/kg bw orally,
- batch 3 was first given glucose at a dose of 75 g/kg bw orally and then dried with ripe fruit juice of *Saba senegalensis* diluted by half, at a dose of 1 mL/100 g bw,
- batch 4 was first given glucose at a dose of 75 g/kg bw orally and then pure juice of ripe fruit of *Saba senegalensis* at a dose of 1 mL/100 g bw,
- batch 5 was first administered glucose at a dose of 75 g/kg bw orally and then AMAREL 3 mg at a dose of 150 mg/kg bw. AMAREL is an oral antidiabetic drug whose active substance is glimepiride.

Following the above treatments, the rats' blood glucose levels were taken for 1 hour ; 2 hours and 3 hours later in each batch using the blood glucose meter.

2.2.6. Statistical analyses

The graphical representation of the effect of *Saba senegalensis* juice on orally induced hyperglycemia was performed using Graph Pad Prism 8.0.1 software. Statistical analysis of the results was performed using analysis of variance (ANOVA ONE WAY). Differences in mean blood glucose levels were determined using the Dunnett Multiple Comparison Test. $P < 0.05$; the difference is significant and $P > 0.05$; the difference is not significant. Blood glucose results were expressed as averages followed by standard deviation.

3. RESULTS

3.1. Determination of trace elements in *Saba senegalensis* juice

The determination of trace elements in the fruit juice of *Saba senegalensis* revealed the presence of calcium, phosphorus, magnesium, potassium, sodium, manganese, zinc, copper and iron with respective contents of 1.20 ± 0.03; 0.42 ± 0.08; 0.95 ± 0.07; 1.40 ± 0.09; 0.09 ± 0.005; 0.27 ± 0.03; 0.96 ± 0.06; 0.94 ± 0.07 and 1.41 ± 0.02 µg/g dry matter (Table I). Among the trace elements measured, iron is the most abundant element (1.41 ± 0.02 µg/g dry matter) followed by potassium (1.40 ± 0.09 µg/g dry matter) while sodium (0.09 ± 0.005) appears to be the least abundant trace element in *Saba senegalensis* fruit juice.

Table I: Trace elements content of *S. senegalensis* juice

Trace elements	**Content (µg/g)**
	***Saba senegalensis* juice**
Calcium	1,20 ± 0,03
Phosphorus	0,42 ± 0,08
Magnesium	0,95 ± 0,07
Potassium	1,40 ± 0,09
Sodium	0,09 ± 0,005
Manganese	0,27 ± 0,03
Zinc	0,96 ± 0,06
Copper	0,94 ± 0,07
Iron	1,41 ± 0,02

3.2. Amino acid determination of *Saba senegalensis* Juice

The HPLC amino acid assay generated a chromatogram (Figure 4) that shows two (02) visible peaks almost confounded and one small, barely visible peak. The retention time (tR), which is the time that elapses between the injection of the sample and the appearance of a peak solute on the detector of the chromatographic column, was 3.047 min for cysteine; 3.168 min for proline and 20.612 min for leucine.

For proline, the test area was 10414333 and the proline control area was 293364. These two areas resulted in a proline content of 35.4997 % in the fruit juice of *Saba senegalensis*. For cysteine, the area generated by the assay was 66422050 and the area generated by the control cysteine was 558567464. These two areas resulted in a cysteine content of 11.8915 in the juice of the fruit of *Saba senegalensis*. For leucine, the area generated by the test was 223762 and the leucine control area was 234866. These two areas determined a leucine content of 0.9527 % in the fruit juice of *Saba senegalensis*. Table II shows the amino acid contents found in the juice of Saba senegalensis and Figure 1 shows their chromatogram.

Table II: Amino acid content of *S. senegalensis* juice

Amino acid	**Retention time (min)**	**Test area**	**Witness area**	**Content (%)**
Cysteine	3,047	66422050	5585674,6415	**11,8915**
Leucine	20,612	223762	234871,4181	**0,9527**
Proline	3,168	10414333	293363,9721	**35,4997**

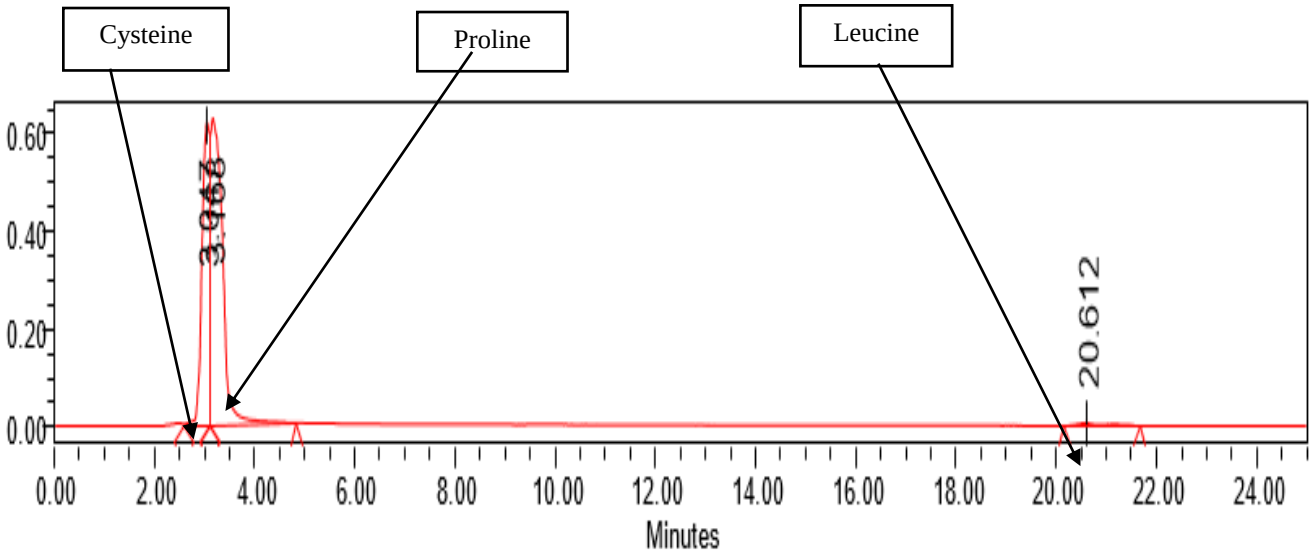

Figure 4 : Chromatogram revealing the presence of cysteine, leucine and proline in the juice of *Saba senegalensis*

3.3. Dosage of vitamins C and B in *Saba senegalensis* fruit juice

Vitamins C and B assays by HPLC generated a chromatogram (Figure 5) which shows two (02) peaks. The retention time (tR), which is the time between the injection of the sample and the appearance of a peak solute on the chromatographic column detector, was 2.425 min for vitamin B1 and 3.079 min for vitamin C.

For vitamin B1, the area generated by the test was 304772 and the control area for vitamin B1 was 910216. These two areas resulted in a vitamin B1 content of 0.3348 % in *S. senegalensis* fruit juice. Concerning vitamin C, the area generated by the trial was 2908104 and the control area for vitamin C was 27574283. These two areas resulted in a vitamin C content of 0.1055 % in the juice of the fruit of *S. senegalensis*. Table III shows the levels of vitamins C and B in *S. senegalensis* fruit juice.

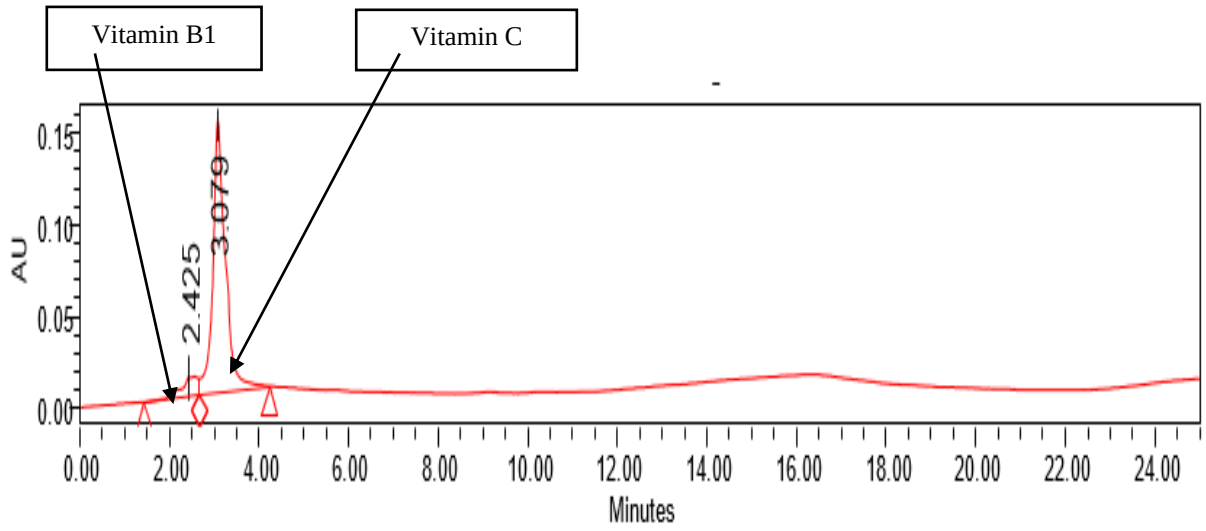

Figure 5 : Chromatogram revealing the presence of vitamins C and B1 in the juice of *Saba senegalensis*

Table III: Vitamin C and B1 content of *S. senegalensis* juice

Vitamins	Retention time (min)	Test area	Witness area	Content (%)
Vitamin C	3,079	2908104	27564966,8246	**0,1055**
Vitamin B1	2,425	304772	910310,6332	**0,3348**

3.4. Effect of *Saba senegalensis* juice on rat blood glucose

Figure 6 shows the effect of *Saba senegalensis* juice and glimepiride on orally induced hyperglycemia. At time zero (time T0), the rats in batch 1 ; 2 ; 3 ; 4 and 5 had an average blood glucose of 65.33 ± 0.88, respectively; 64.67 ± 1.20; 65.67 ± 1.76; 64.33 ± 1.45 and 66.00 ± 1.53 mg/dL.

One hour (time T1) after glucose administration followed by treatment with distilled water (batch 2), rats in batch 2 had a mean blood glucose level of 95.33 ± 0.88 mg/dL. This blood glucose in the rats in batch 2 was very highly significant ($P < 0.001$) compared to that (65.33 ± 0.88 mg/dL) in the control batch (batch 1) rats that did not receive glucose. In the rats in batch 3 that received glucose and were treated with *S. senegalensis* juice diluted by half, their mean blood glucose was 85.33 ± 0.88 mg/dL at time T1 and was highly significant ($P < 0.01$) compared to the blood glucose (65.33 ± 0.88 mg/dL) of the rats in batch 1. In the rats in batch 4 that received glucose and were treated with pure *S. senegalensis* juice, their mean blood glucose was 74.33 ± 1.45 mg/dL at time T1 and had a significant increase ($P < 0.05$) compared to the blood glucose (65.33 ± 0.88 mg/dL) of the rats in batch 1. For rats in Batch 5 that received glucose and were treated with Amarel (glimepiride), their mean blood glucose was 73.67 ± 1.76 mg/dL at time T1 and had a significant increase ($P < 0.05$) compared to the blood glucose (65.33 ± 0.88 mg/dL) of the rats in batch 1.

Two hours (time T2) after glucose administration, blood glucose (107.30 ± 1.20 mg/dL) in rats in batch 2 increased extremely significantly ($P < 0.0001$) compared to that (65.00 ± 0.58 mg/dL) in Rats in Batch 1 at time T2. Blood glucose (93.67 ± 1.20 mg/dL) in rats in batch 3 at the second hour was highly significant ($P < 0.01$) compared to blood glucose (65.00 ± 0.58 mg/dL) in rats in batch 1 at the 2nd hour. Concerning the rats in batches 4 and 5, they had mean blood glucose levels of 70.00 ± 0.58 mg/dL and 68.33 ± 0.33 mg/dL respectively at the 2nd hour. These blood glucose levels normalized ($P > 0.05$) because they were close to that (65.00 ± 0.58 mg/dL) of the rats in batch 1 at the 2nd hour.

At the third hour (time T3), the blood glucose levels of the rats in batch 4 (65.33 ± 0.33 mg/dL) and those (66.67 ± 1.20 mg/dL) in the rats in batch 5 remained normal ($P > 0.05$) compared to those (65.33 ± 0.88 mg/dL) in the rats in batch 1. Also, the blood glucose levels of the rats in batch 4 (65.33 ± 0.33 mg/dL) and those (66.67 ± 1.20 mg/dL) of the rats in batch 5 at the 3rd hour were similar ($P > 0.05$) to their basal blood glucose levels (time T0) which were 64.33 ± 1.45 and 66.00 ± 1.53 mg/dL respectively.

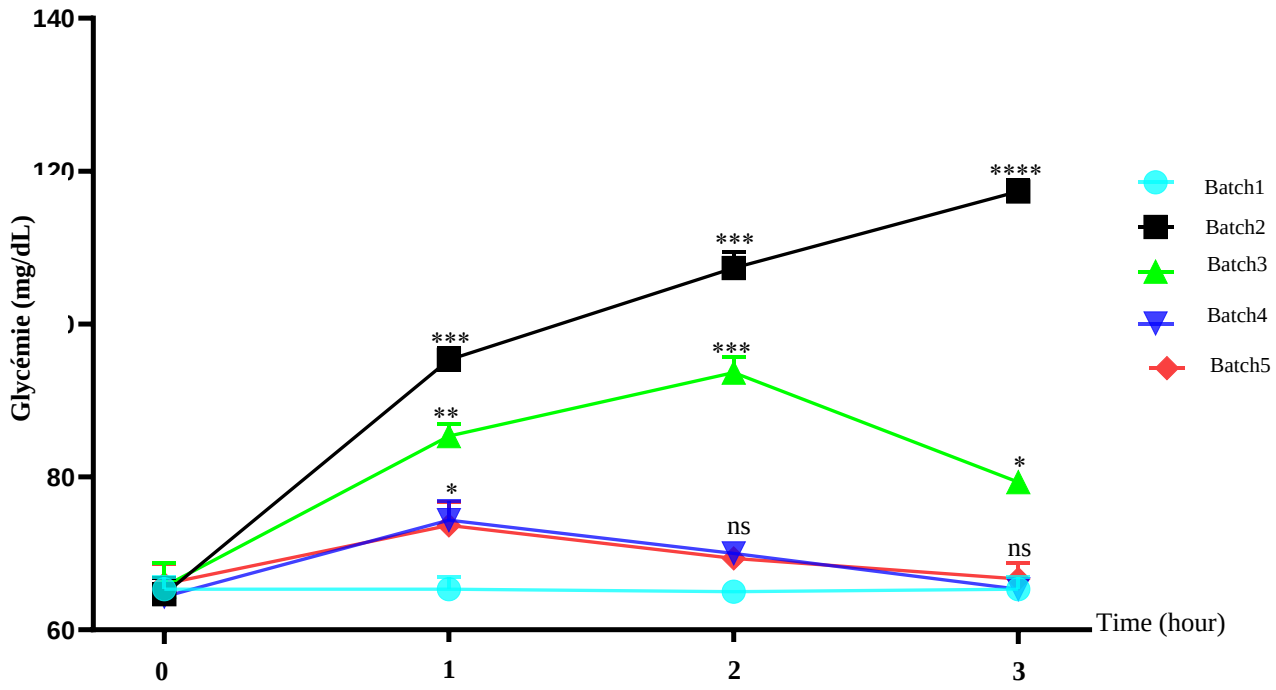

Figure 6 : Effect of *Saba senegalensis* juice on orally induced hyperglycemia

ns : non-significant difference compared to the control rat batch
*** :** significant difference compared to the control rat batch
**** :** highly significant difference compared to the control rat batch
***** :** very highly significant difference compared to the control rat batch
****** :** extremely significant difference compared to the control rat batch
Batch$_1$: rats not receiving glucose and treated with distilled water
Batch$_2$: rats given glucose and treated with distilled water
Batch$_3$: rats given glucose and treated with *S. senegalensis* juice diluted by half
Batch$_4$: rats given glucose and treated with pure juice of *S. senegalensis*
Batch$_5$: rats given glucose and treated with Glimepiride

4. DISCUSSION

The micronutrient assay revealed the presence of calcium, phosphorus, magnesium, potassium, sodium, manganese, zinc, copper and iron in the juice of ripe fruit of *Saba senegalensis*. This presence of trace elements in the juice of ripe fruit of *Saba senegalensis* would find their application in oligotherapy, which is an alternative medicine practice, consisting of food supplements with trace elements[7].

As for amino acids, their quantification in the juice of ripe fruit of *Saba senegalensis* revealed the presence of cysteine, proline and leucine. Leucine is an essential amino acid that cannot be synthesized by the body and must therefore be provided through the diet, which is necessary for the proper functioning of the body[8].

The presence of vitamins C and B1 (thiamine) in *Saba senegalensis* fruit juice is in line with the results of Sarr et al. who found these two vitamins (C and B1) during their work on the pulp of *Saba senegalensis* harvested in Senegal[9].

Glucose uptake by the rats induced two phases. A phase of hyperglycemia in rats that ingested glucose and did not receive treatment and a phase of normalization of blood glucose in rats that ingested glucose and treated with *Saba senegalensis* juice or glimepiride (AMAREL's antidiabetic active substance). Indeed, after a meal, the sugars contained in food tend to increase blood sugar levels. This is called postprandial blood glucose. This increase in blood sugar is mainly controlled by insulin secretion, which induces the storage of glucose in the liver; the uptake and storage of glucose in the muscles and in adipose tissues (triglycerides): this is known as carbohydrate homeostasis [10]. In addition, after a meal, part of the glucose present in the blood is directly used by the cells to produce energy: this is glycolysis [11].

The lowering and normalization of blood glucose levels in the treated rat batches could be explained by the presence of trace elements, amino acids and vitamins in *Saba senegalensis* fruit juice. As far as trace elements are concerned, zinc, magnesium and iron are involved in the regulation of blood sugar levels. Zinc is involved in the storage and secretion of insulin, which is a hypoglycemic hormone. Zinc intervenes, first of all, on the structure of insulin and also on the binding of insulin to its receptor. It is absorbed in the small intestine, more precisely in the jejunum. During a meal, zinc is captured at the brush edge of the digestive epithelium by amino acids such as cysteine[12]. As for magnesium, it stabilizes the action of insulin because a magnesium deficiency would disrupt the action of insulin by causing insulin receptors to malfunction[11]. As for iron, it plays a role in the degradation of insulin because its deficiency slows down this degradation and leaves insulin in the blood longer. This state of hyperinsulinemia leads to episodes of hypoglycemia [11]. The lowering and regulation of blood sugar is thought to be linked to the presence of amino acids such as cysteine in the juice of ripe *Saba senegalensis* fruit. Indeed, cysteine allows the uptake of zinc, but zinc, in addition to being a powerful antioxidant, has an insulin-protective action and activates the kinases involved in insulin signaling and phosphorylations necessary for insulin efficiency[13]. As regards vitamins, the presence of vitamin C in Saba senegalensis fruit juice helped to normalise blood sugar levels in rats treated with *Saba senegalensis* juice. Indeed, the antioxidant capacity of vitamin C promotes the reduction of insulin resistance and has better glycemic control [11]. The mechanism of action of pure juice from ripe fruits of *Saba senegalensis* is thought to stimulate the release of insulin by beta cells from the pancreatic islets. This effect is thought to be based on an increase in the response of beta pancreatic cells to the physiological glucose stimulus. Pure juice from ripe fruit of *Saba senegalensis* mimics the action of glimepiride, an oral antidiabetic drug belonging to the sulfonylurea family[14], used in this study as a reference molecule.

5. CONCLUSION

At the end of the study, it appears that *Saba senegalensis* fruit juice contains trace elements (calcium, phosphorus, magnesium, sodium, manganese, zinc, copper, iron and potassium), amino acids (cysteine, proline and leucine) and vitamins (C and B1). Like glimepiride : a reference antidiabetic molecule marketed under the name AMAREL, the pure juice made from the ripe fruits of *Saba senegalensis* regulated the hyperglycemia caused orally in *Rattus norvegicus*. Pure juice of ripe fruits of *Saba senegalensis* could be advised as a nutraceuticalum in episodes of hyperglycemia. Therefore, it is therefore advantageous to consume the juice pure from the ripe fruits of *Saba senegalensis*. Pure juice of ripe fruits of *Saba senegalensis* could be advised as a nutraceuticalum in episodes of hyperglycemia. In perspective, it would be important to evaluate the effect of ripe fruit juice of *Saba senegalensis* in rats made diabetic.

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