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Research Article

EVALUATION OF ANTIDIABETIC ACTIVITY OF AQUEOUS EXTRACTS OF FORMULATIONS PRODUCED FROM LEAFY VEGETABLES AND *SOUMBARA* IN RATS

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A B S T R A C T

In Sub-Saharan Africa and more particularly in Côte d'Ivoire, many ethnobotanical studies have shown the pharmacological activities of the genera Leptadenia, Ocimum and Parkia against diabetes. Formulations made from leafy vegetables (Leptadeniahastata, Ocimumgratissimum) and soumbara are a very interesting and valuable natural source of valuable bioactive compounds that can be beneficial in the prevention of diabetes and its complications. In this context, the objective of this study is to evaluate the toxicity and to estimate the possible antidiabetic effect of the aqueous extracts of the various formulations on the weight and the glycaemia in rats rendered diabetic by alloxan. Before looking for the potential antidiabetic effect in vivo, an analysis of acute oral toxicity in rats was undertaken. The results showed that no mortality and no clinical signs of toxicity were observed in all rats. The lethal dose (LD50) obtained was greater than 5000 mg/kg bw, which made it possible to classify the aqueous extracts in category 5 of non-toxic substances by the oral route. After induction of diabetes, treatment with aqueous extracts of the different formulations was administered to diabetic rats orally at a daily dose of 50, 100 and 200 mg/kg for 28 days. The results obtained showed a marked increase in the body weight of the rats from -3.39% to 3.96%; 0.06% to 5.96% and 0.25 to 6.58% of baseline weights, respectively for doses of 50, 100 and 200 mg/kg bw and a significant drop in blood glucose ($p < 0.01$) from 41.94 to 49.53% in rats treated with the aqueous extract at a dose of 50 mg/kg bw; from 56.43 to 65.03% in rats treated with the aqueous extract at a dose of 100 mg/kg bw and from 60.86 to 68.89% in rats treated with the aqueous extract at a dose of 200 mg/kg bw, compared to diabetic control rats. However, the F2 and F3 formulations at doses of 100 and 200 mg/kg bw showed better antidiabetic activity. In conclusion, the present study suggests that the aqueous extract of the F3 formulation at the dose of 200 mg/kg bw has a beneficial effect on the control of diabetes by protecting these rats against the massive loss of body weight and by significantly reducing the blood sugar.

INTRODUCTION

Diabetes is one of the fastest growing epidemics of the century. An insidious pathology by definition, diabetes shows a more than worrying epidemiological transition. According to some projections, 600 million people, including 42 million in Africa, will suffer from it by 2030 (FID, 2019). This figure is expected to increase by 129% to reach 55 million by 2045 (WHO, 2022). In addition to these alarming figures, it is necessary to take into account people who are unaware that they are diabetic because the development of the pathology is silent and sneaky (30 to 80% of people with undiagnosed disease) (Beagley *et al*., 2014). Once considered a disease of developed countries, in Sub-Saharan Africa where malnutrition and junk food coexist, diabetes mellitus is already responsible for nearly 9% of deaths, with numerous disabling complications: cardiovascular disease, kidney failure, diabetic coma. It is the leading cause of blindness and accounts for more than 50% of non-traumatic amputations in this part of the world (Ekoé, 2004; Akré *et al*., 2021). The complications of diabetes can require lifelong treatment for the patient, which is expensive for populations in poor countries, which

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have limited access to chemical drugs. However, the excessive cost of these chemical drugs and the lack of medical infrastructure, combined with the lack of medical personnel in Africa, are leading people to turn to traditional medicine (Onsiyor *et al*., 2019). The Republic of Côte d'Ivoire, like other African countries on the one hand, and those around the world on the other hand, is not spared by this pandemic. In Côte d'Ivoire, data on diabetes are not updated. In 2019, the national program for the fight against metabolic diseases and the prevention of non-communicable diseases (PNLMM/PMNT) revealed that the prevalence of diabetes in Côte d'Ivoire is 6.2%, or more than seven hundred thousand (700,000) people with diabetes. Thus, faced with this problem, the search for new bioactive, effective and inexpensive molecules against this pathology is essential. Volunteer food plants are a good alternative for making improved traditional medicine or isolation of molecule of therapeutic interest (Pari and Venkateswaran, 2002; N'diaye, 2008). The aqueous extracts of the leaves, fruits, roots or bark of these plants are regularly administered in the form of decoction, infusion or macerate by local populations for the treatment of diabetes (Kamalrudinet al., 2018;Embeya *et al*., 2020; Djike *et al*., 2022). According to Jin *et al*. (2008), diabetologists have come to the evidence that a therapeutic supplement consisting of plant extracts is necessary to optimize the treatment of diabetes. As a result, food extracts formulated with traditional leafy vegetables and fermented seeds of Parkia biglobosa (soumbara) could be an alternative to this nutritional disorder. Indeed, traditional leafy vegetables are excellent sources of micronutrients and antioxidants (Bajpai et al., 2005;Itoua et al., 2015), as well as the dried fermented seeds of Parkia biglobosa (soumbara) which are known for their nutritional and therapeutic importance (Coulibaly *et al*., 2017; Cissé *et al*., 2021). In sub-Saharan Africa and more particularly in Côte d'Ivoire, many ethnobotanical studies have shown the pharmacological activities of the Leptadenia, Ocimum and Parkia genera against diabetes (Tra Bi *et al*., 2008;Bouaré, 2022).Thus, their intake in humans could help in the prevention and treatment of diseases linked to oxidative stress such as diabetes (Patrick, 2005;Ehilé *et al*., 2018).

In addition, different formulations have been developed by some researchers (Soro *et al*., 2013; Touré *et al*., 2019; Angamanet al., 2021), to our knowledge, no study on the antidiabetic activity of these formulations was not conducted. The objective of this work is to evaluate the antidiabetic properties of aqueous extracts of formulations produced from traditional leafy vegetables and soumbara in order to contribute to the improvement of the nutritional and health status of Ivorian populations.

MATERIAL AND METHODS

Biological material

The biological material used in this study consists of fresh leaves of 02 species of leafy vegetables and fermented seeds of Parkia biglobosa. These are *Leptadeniahastata*(zongnê) and *Ocimumgratissimum* (mangnrin). They were collected in fields located in the departments of Korhogo (north latitude: 09°27'41"; west longitude: 05°38'19") and Dabakala (north latitude: 08°23'; west longitude: 04 °26') (Ivory Coast). These sheets were authenticated at the Centre National de Floristique of the University Félix Houphouët-Boigny (Abidjan, Côte d'Ivoire). The fermented seeds of *Parkia biglobosa* (*soumbara*) were purchased at the big market in Korhogo.

Animal material

The animal material consists of albino rats (Rattus norvegicus) of the Wistar strain weighing between 120 and 180 g provided by the Pasteur Institute of Côte d'Ivoire in Adiopodoumé.

Chemical products

The reagents and chemicals used in this work are of analytical grade. Alloxan monohydrate and 5% anhydrous glucose (SIGMA ALDRICH ®, USA); glibenclamide: GLIDIABET® (FERRER INTERNATIONAL S.A. SPAIN); anhydrous glucose (Chengdu ZHONGCHENG CHEMICAL Co., Ltd., CHINA); isotonic salt water 0.9%; distilled water.

METHODS

Processing of leafy greens

The treatment of leafy vegetables was carried out according to the method described by Chinma and Igyor (2007). After collecting them, the various leafy vegetables were immediately transported to the Biotechnology and Agroresources Transformation Laboratory of the Peleforo Gon COULIBALY University in Korhogo where they were sorted, cleared of debris, detached from their stems and rinsed with distilled water. They were then drained at laboratory temperature (20°C).

Steam cooking

Steaming was carried out according to the method described by Barkat and Kadri (2011). Five hundred (500) grams of fresh leaves were introduced into a couscous maker connected to a stainless steel pot containing 1.5 L of demineralized water previously brought to the boil. The leaves were blanched for 5 min. After cooking the leaves were drained and cooled to room temperature.

Shade drying

Drying in the shade was carried out according to the method described by Mepba *et al*. (2007). The bleached leaves were spread on laboratory benches covered with plastic bags (25-28°C) for 15 days. The dried leaves were ground using a micro grinder (CULATTI, France) equipped with a sieve (10 µm) and were stored in the freezer at 4°C.

Treatment of fermented seeds of *Parkia biglobosa* (*soumbara*)

One Kilogram (1Kg) of fermented and dried Parkia biglobosa seeds (soumbara) was roasted between 120-150°C for 10 minutes. The roasted seeds were cooled to room temperature then ground using a micro-grinder (CULATTI, France) equipped with a sieve (10 µm) and stored in the freezer at 4°C.

Formulation of food supplements

The formulation of food supplements was carried out according to the method of Touré *et al*. (2019).The formulations were made with the bleached and dried leaves of *Leptadeniahastata*, *Ocimumgratissimum* and *soumbra*. Table 1 below presents the proportions of the leaves and the *soumbara*of the different formulations.

Table 1: Proportions of leaves and soumbara of the different formulations

Formulations	***L. hastata***	***O. Gratissimum soumbara***	**Total Quantity (g)**	
F1	47,5	47,5	5	100
F2	45	45	10	100
F3	42,5	42,5	15	100
F4	40	40	20	100
F5	37,5	37,5	25	100

Preparation of the aqueous extracts of the different formulations

The aqueous extract was obtained according to the method described by Zihiri *et al*. (2003).One hundred grams (100 g) of powder of each formulation were mixed for 24 hours in 1 liter of distilled water under magnetic stirring. Each homogenate was successively filtered twice on absorbent cotton, then once on whatman N°3 paper. The filtrates collected are steamed at 60° C. for 6 days. The powder obtained was stored at 4° C. for possible analyses.

Assessment of the acute toxicity of aqueous extracts

Acute toxicity was investigated using the Organization for Economic Co-operation and Development Guideline 423 **(**OECD, 2001). Sixty (60) rats weighing between 150 and 180 grams on average were used for the experiment. The fingerlings were carefully weighed then divided into 4 batches of 3 fingerlings each. Thus, three (03) rats, deprived of food during the night, but no water, are weighed, then received orally 1 mL of the aqueous extract at a dose of 300 mg/kg bw in a single dose. using an intubation cannula. After administration of the aqueous extract, the three rats are again fasted for 3 hours. They are observed individually for the first 30 minutes and regularly for the first 24 hours. If no effect of the extracts is observed, the rats are then observed daily for the 14 days of exposure. Observations focused on changes in skin, hair, salivation and behavior. Twenty-four (24) hours after administration of the 300 mg/kg bw dose, if no mortality and no moribund state have been observed, the 2000 mg/kg bw dose is tested. After administration of this dose, if no mortality and no moribund state have been observed, the dose of 5000 mg/kg bw is tested under the same conditions. The control batch (batch T) composed of three rats received distilled water instead of the extracts.

Induction of Diabetes in Wistar Rats

Diabetes was induced by injection of a solution composed of alloxan monohydrate(Sigma-Aldrich) with saline (0.9%) according to the method described by Ahmad *et al*. (2016). Eighty-five (85) male Wistar rats were fed water for 14 hours. They received intraperitoneally a single dose of 150 mg/kg body weight (bw) of the freshly prepared alloxan solution. After induction, the rats received an anhydrous glucose solution (5%) overnight in order to overcome the hypoglycemic shock induced following the action of alloxan. Seventy-two hours (72h) after the injection, a blood sample was taken by caudal amputation in order to measure the glycaemia. Rats with blood sugar levels above 200 mg/dL and showing clinical signs such as polyuria, polydipsia and polyphagia are considered to be diabetic and were retained for the rest of the experiment.

Treatment of rats

Ninety (90) rats were weighed (120-150 g) and divided into 4 groups. The first three batches consisted of 5 rats each. The last batch (75 rats) was subdivided into 5 sub-batches of 15 rats each and the treatment was carried out over a period of 28 days.

Batch 1 consisted of normoglycemic control rats (TNG), receiving two (02) mL of distilled water throughout the duration of the experiment. Batch 2 consisted of diabetic control rats (TD), treated with two (02) mL of distilled water throughout the experiment. Group 3, made up of diabetic rats, received a daily dose of 10 mg/kg bw of glibenclamide (Glib), the reference hypoglycemic substance (R-Glib). Batch 4 divided into 5 sub-batches included diabetic rats which were force-fed daily with two (02) mL of aqueous extracts F1, F2, F3, F4 and F5 at doses of 50, 100 and 200 mg/kg bw at a rate of 5 rats per dose. These doses were chosen following the preliminary tests carried out as part of this study.

Evaluation of the effect of aqueous extracts of formulated foods on body weight

Measurements of the body mass of the treated rats and of the controls were made each week throughout the experiment, using an electronic scale (SARTORIUS) and the variations in the body weight of the rats compared to the 1st day were expressed as a percentage (%) and calculated according to the following formula:

Changes in body weight (%) = Wd- Wd_0 X 100 / Wd_0
Wd_0: body weight on day 1; **Wd**: body weight on D-Day.

Evaluation of the effects of aqueous extracts of formulated foods on glycaemia

Blood glucose measurements were taken weekly for 4 weeks. They were determined for each lot at regular time intervals using an ACCU-CHEK Active brand strip glucometer on a drop of blood taken from the tail end of the rats (venous blood). Changes in blood glucose were calculated using the following formula:

Variations in blood glucose= (BS_x x 100 / BS_1) – 100
VBS = Variations in blood glucose; **BS_x** = Blood glucose value on day x, x = Sampling day;
BS_1= Blood glucose value on day 1.

Statistical analysis

Statistical data processing and graphical representation is performed using Graph Pad Prism 9.5.1 software (San Diego, California, USA). The values were given as means followed by the standard error on the mean (M ± SEM). Statistical analysis of the results was performed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test, with a significance level $P < 0.05$.

RESULTS AND DISCUSSION

Evaluation of the acute toxicity of the aqueous extracts of the different formulations

For the different formulations, at a dose of 300 mg/kg bw, the rats showed no signs of toxicity after administration of the different extracts. There is no change in mobility, behavior, appetite. No mortality was observed. These observations were made after three hours and for 14 days, after the

administration of the product. At a dose of 2000 mg/kg bw, the rats drag their front legs but remain mobile. However, there were no fatalities. After high water consumption, the signs mentioned disappeared. At a dose of 5000 mg/kg bw, the rats were exhausted and weakened but returned to their normal state after 2 days. Our results are consistent with those reported by Etame-Loe *et al.* (2018) and Nyangono *et al.* (2023) who respectively showed that during their work, the aqueous extracts combined with palm wine from the bark of the trunk of *Musangacecropioides* and the fruits of *Combretum micranthum*, and those of *Caloncobaechinata* and *Cesariabarteri* did not cause any toxic effect at a dose of 5000 mg/kg. Authors attest that the leaves (*L. hastata* and *O. gratissimum*) as well as the *soumbara*used as ingredients of our formulations, are consumed as vegetables in West Africa thanks to their bio-tolerance (Vodouhé *et al.*, 2012; Cissé *et al.*, 2021; Coulibaly *et al.*, 2022).

Effect of aqueous extracts of different formulations on the body weight of diabetic rats

The body weight of the different batches of rats during the period of the experiment (28 days) is presented in figure 1.

From the 1st to the 28th day, the results revealed a very significant decrease ($P < 0.01$) in body weight of the batch of untreated diabetic rats (120.53±1.73 g to 96.60±1.69 g) compared to the batch of normoglycemic control rats (120.36±1.67 g to 133.13±1.59g). Indeed, intraperitoneal injection of alloxan in normal rats effectively induces diabetes, which results in a loss of body weight that can lead to several diabetes-related complications (Boudjelal *et al.*, 2011). Our results are in agreement with the work of Shah *et al.* (2019) who found that, in male rats of the Wistar strain, the injection of Streptozotocin (STZ) caused after four weeks a significant decrease in body weight.

This significant weight loss of 19.84% observed in diabetic control rats (DT) could be related to the intensive catabolism of lipids and structural proteins used as an energy source due to the unavailability of carbohydrates (Krishnasamy, 2013). It could also be attributed to insulin deficiency, which has the effect of a consequent reduction in protein synthesis, resulting in a decrease in the absorption of amino acids by the tissues, which would slow down growth and lead to muscle atrophy (Ajiboye *et al.*, 2019).

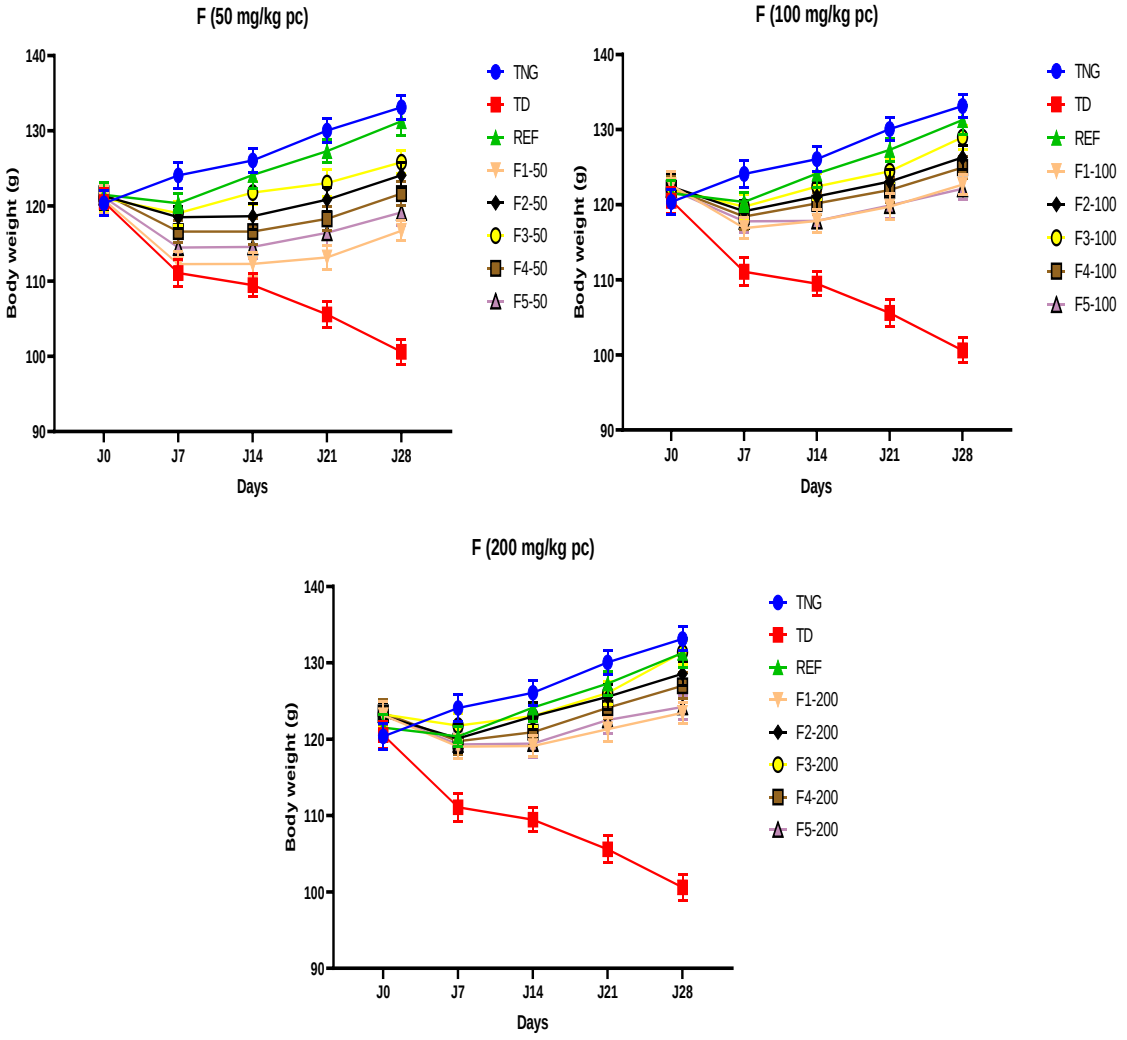

Figure 1: Evolution of body weight after treatment of rats with the different formulations at doses of 50, 100 and 200 mg/kg bw

TNG: Normoglycemic control rat; DT: Diabetic control rat ; REF : Rat treated with the reference substance (glibenclamide) ; F1 : Formulation 1 ; F2 : Formulation 2 ; F3 : Formulation 3 ; F4 : Formulation 4 ; F5 : Formulation 5 ; 50 : 50mg/kg dose ; 100 : 100 mg/kg dose and 200 : 200 mg/kg dose.

Furthermore, the results obtained revealed an increase in weight in the normoglycemic control rats (120.36±1.67 g to 133.13±1.59 g), i.e. an increase of 10.61%, linked to animal growth. However, oral administration of the aqueous extracts of the different formulations at doses of 50 mg/kg induced an increase in weight (-3.39% to 3.96%); 100 mg/kg (0.06% to 5.96%) and 200 mg/kg bw (0.25% to 6.58%) based on initial weight (P<0.01). A restoration of body weight is also observed in the diabetic group treated with glibenclamide with an increase of 8.05% compared to the initial weight (P < 0.01). Our results are in agreement with those published by Hussaini*et al.* (2018) and Boudiaf (2020).These authors respectively found that after 2 and 3 weeks of treatment, the oral administration of the aqueous extract of *Spirulina platensis* and of cinnamon and quercetin induced a remarkable increase in the weight of the treated diabetic rats. In contrast, the ability of aqueous extracts of the different formulations to protect diabetic rats from massive body weight loss may be due to their ability to improve glycemic homeostasis by reducing plasma lipid levels and inhibiting the gluconeogenesis pathway (Mollica *et al*., 2017; Embeya *et al*., 2020).

Effects of the aqueous extracts of the different formulations on the glycaemia of diabetic rats

The values of the different blood glucose levels taken are recorded in Figure 2. The results show on the 28th day of the experiment, a significant difference (P< 0.01) between the blood glucose levels of the untreated diabetic group (399.54 ± 5.36 mg /dL, i.e. an increase of 22.77%) and the blood sugar of the healthy control group (97.06±5.25 mg/dL, i.e. a decrease of 0.06%). This result confirms the onset of diabetes after the injection of alloxan. The latter is a diabetogenic product with toxicity on the β cells of the islets of the pancreas via the glucose transporter, GLUT2 (Matteucci and Giampietro, 2008).

The results obtained in this study showed that the average glycaemia of diabetic rats without treatment is nearly 3 to 4 times higher than that of normoglycemic rats. Our results are consistent with those of Jdir (2017) and Bédou (2019) who induced diabetes in rats by intraperitoneal injection with alloxan. On the other hand, at the end of the 28 days of experimentation, the results reveal a significant drop in glycaemia (P < 0.01) after the treatment of diabetic rats with doses 50 (197.52±5.19 (F1) at 172.09±5.79 mg/dL (F3), a decrease of 41.94 to 49.53%); 100 (144.97±5.77 (F1) to 116.43±5.22 mg/dL (F3), a decrease of 56.43 to 65.03%) and 200 mg/kg bw (134.20 ±5.02 (F1) to 106.72 ±5.36 mg/dL (F3), i.e. a decrease of 60.86 to 68.89%) of the different formulations, as well as with the reference medicine, the glibenclamide (106.33±5.02 mg/dL, a decrease of 67.75%). The blood sugar of the treated rats was 2 to 3 times lower than that of the untreated rats. These results are in agreement with those reported by Djiké *et al*. (2022) who obtained with the aqueous extract of the trunk bark of *Sclerocaryabirrea* (Anacardiaceae) a greater drop in blood sugar (68%) than that of glibenclamide (65.52%). However, the analysis of the results did not show any significant difference between the

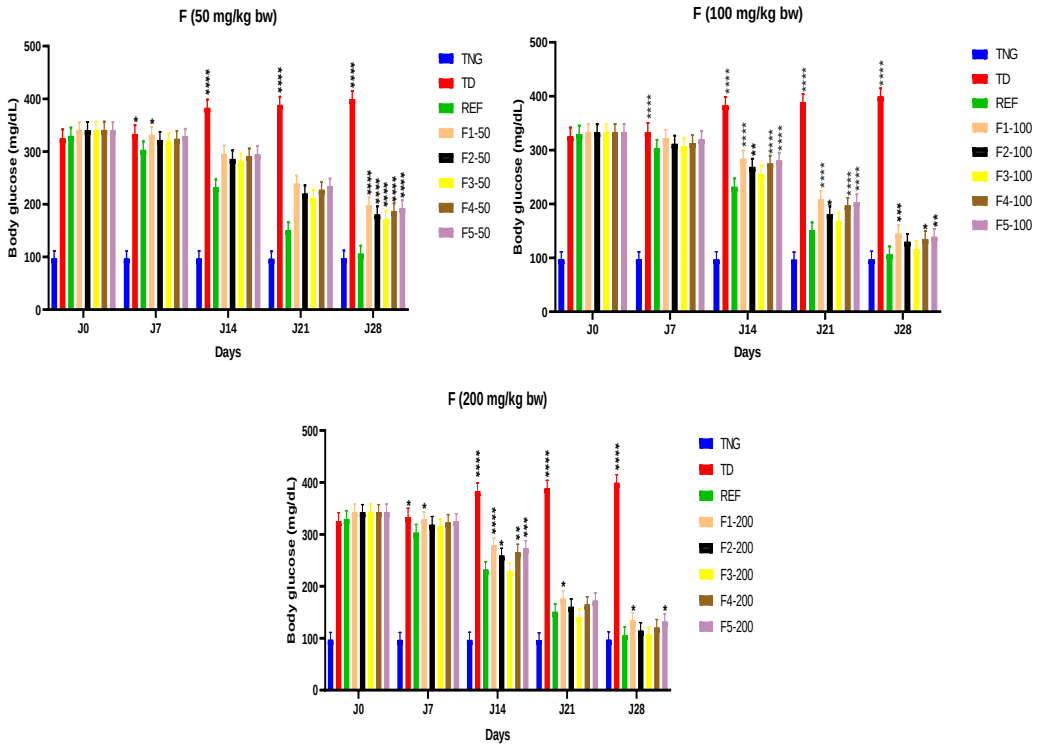

Figure 2 : Evolution of glycaemia after treatment of rats with the different formulations at doses of 50 mg/kg, 100 mg/kg and 200 mg/kg bw

**p<0.05; **p<0.01; ***p<0.001; ****p<0.0001 = significant difference between the batch of rats treated with the reference substance (glibenclamide) and the batches of non-diabetic and diabetic rats treated or not with the extracts; TNG: Normoglycemic control rat; DT: Diabetic control rat; REF: Rat treated with the reference substance (glibenclamide); F1: Formulation 1; F2: Formulation 2; F3: Formulation 3; F4: Formulation 4; F5: Formulation 5; 50: 50mg/kg dose; 100: 100 mg/kg dose and 200: 200 mg/kg dose.*

glycaemia of the rats treated with the reference substance (glibenclamide) and those of the rats treated with the aqueous extracts F2 and F3 at the dose of 100 and 200 mg/kg pc. Indeed, the drop in glycaemia observed in treated diabetic rats shows that the aqueous extracts of our different formulations (F2 and F3) at doses of 100 and 200 mg/kg bw, would possess antidiabetic activity as mentioned by Bédou *et al*. (2018) in their study on the hypoglycemic and anti-hyperglycemic activities of the fruits of Bauhinia thonningii (Caesalpiniaceae) on rats rendered diabetic by alloxan. This antidiabetic activity would be due on the one hand to the concentration of the various metabolites inherent in the composition of our extracts (polyphenols, flavonoids, etc.) and on the other hand to their activity. This finding was confirmed by the work of Mbiyangandu Kadiata *et al*. (2022) in the phytochemical study of some food and medicinal plants used in the prevention and treatment of type 2 diabetes in the Democratic Republic of Congo.

CONCLUSION

Evaluation of the antidiabetic effect of the extracts of the different formulations at doses of 100 and 200 mg/kg bw in rats enabled them to be protected against massive loss of body weight and significantly reduced their blood sugar levels. Our results support, indeed, the motivation of the recourse to traditional medicine by the users of plants. These formulations produced from leafy vegetables and soumbara, in particular the F3 formulation at a dose of 200 mg/kg bw, could therefore play a role as a food supplement for preventive purposes or contribute to the management of diabetes. However, more advanced studies are still recommended to deepen not only the knowledge of the different polyphenols and flavonoids with this antidiabetic activity.

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