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(RESEARCH ARTICLE)

Effects of aqueous extracts of *Annona senegalensis* and *Hallea ledermannii* on hepatic and pancreatic histological architecture in diabetic Wistar rats

Gooré Guy Charles Golé NANTI [1,*], Bi Lané Andrien GOH [2], Kouehiouon Justin Anderson-Bel DJIKE [3] and Bi Semi Anthelme NENE [4]

[1] *Department of Genetics, Biology and Animal Physiology, Faculty of Agroforestery, Agro valorisation Laboratory, Jean Lorougnon Guédé University, BP 150Daloa, Ivory Coast.*
[2] *Department Animal Biology, Faculty of Biological Sciences, Péléferon Gon Coulibaly University,BP 1328 Korhogo, Ivory Coast.*
[3] *Department Animal Biology, Faculty of Sciences and Technologies, Laboratoire Sciences de Biologie Animale, Alassane Ouattara University, BPV 18 Bouaké 01, Ivory Coast.*
[4] *Department of Applied Biology and Health, Faculty of Biosciences, Biology and Health Laboratory, Félix Houphouët Boigny University, 22 BP 582 Abidjan 22, Ivory Coast.*

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Abstract

Background: Diabetes mellitus is a disease that causes numerous organ malfunctions in animals.The prohibitive cost of modern medicines for populations in developing countries is directing patients suffering from this pathology towards phytotherapy. A preclinical study of herbal remedies is therefore highly desirable.

Objective: The aim of this study was to evaluate the impact of aqueous extracts of *Annona senegalensis (Annonaceae)* (EAAs) and *Hallea ledermannii (Rubiaceae)* (EAHl) on the liver and pancreas of diabetic Wistar rats.

Methodology: Induction of diabetes mellitus in normal rats with body weights ranging from 200 to 250 g was achieved by intraperitoneal injection of alloxane (75 mg / kg bw). After four (4) and thirteen (13) weeks of treatment, some diabetic rats were sacrificed by decapitation following ethyl urethane anesthesia (Bouafou, 2007). The liver and pancreas of these rats were dissected to determine their relative weight, followed by histological analysis.

Results: After four (4) and thirteen (13) weeks of treatment, the relative liver and pancreas weights of all these test animals did not change significantly compared with those of non-diabetic rats. At four (4) weeks of treatment, histological analysis of the liver revealed lesions of diffuse moderate glycogen overload in the liver parenchyma and hepatocyte apoptosis in rats treated with EAAs (100 and 200 mg / kg bw), EAHl (200 and 400 mg / kg bw) and Glibenclamide (10-2 g / kg bw). In the pancreas of test rats, histological studies showed that the islets of Langerhans of diabetic rats treated with plant extracts were necrotic and affected by apoptosis, compared with those of non-diabetic rats. Severe lymphocytic chronic pancreatitis was also observed in this organ of these animals. After 13 weeks (J91) of treatment, histological sections of the pancreas of diabetic rats treated with glibenclamide and our natural substances showed a normal pancreas with islet regeneration comparable to that of normal rats.

Conclusion: This study highlighted the pancreatic regenerative activities of EAAs and EAHl in diabetic rats.

Keywords: *Annona Senegalensis; Hallea Ledermannii*; Histology; Liver; Pancreas; Rat; Diabetes

* Corresponding author: Gooré Guy Charles Golé NANTI

1. Introduction

Diabetes is a serious metabolic disease that is increasingly threatening public health worldwide. It affects around 4% of the world's population, and is expected to increase to 5.4% by 2025 (Al- Achi A., 2005). In certain traditional, non-industrialized societies (China, certain African and Latin American countries, etc.), the medicinal management of so-called chronic pathologies (diabetes, hypertension) is largely ensured by the use of medicinal and food plants (Sharma et al., (2008); Guermaz et al., (2008); Singh et al., (2009); Zhou et al., (2009)). The existence of a traditional anti-diabetic pharmacopoeia for the treatment of diabetic pathology is widespread, and its existence is confirmed by the practitioners and doctors who practice it (Sharma et al., (2008); Singh et al., (2009)). Plants are recognized as a wonderful source of medicines. Currently, 1200 species of plants are used as medicines in traditional diabetes therapy (Marles et al., 1995). However, for most of them, the scientific evidence is not yet clear. With this in mind, we set out to study the effects of aqueous extracts of *Annona senegalensis (Annonaceae)* (EAAs) and *Hallea ledermannii (Rubiaceae)* (EAHl), two plants from the traditional African pharmacopoeia used in the treatment of diabetes (Lawin et al., (2016); Njapdounke et al., (2016)). According to Yeo et al., (2011), *Annona senegalensis* leaf extract reduces the number of inflammatory cells. According to the work of Konate et al., (2012), the Aqueous extract of *Annona senegalensis* root bark is used as an anticonvulsant. *Hallea ledermannii* is used as a local anesthetic, lowering blood pressure and regulating disorders of the intestinal lymphatic system. Studies (Burkill et al., (1997); Diallo et al., (1995)) have shown that this plant possesses anti-tumor activity. The general aim of this study is to evaluate the hepatoprotective properties and pancreatic regenerative activity of EAAs and EAHl in diabetic Wistar rats. This was achieved by assessing the impact of these plants on certain vital organs in these diabetic animals. The acute toxicity study of these plant extracts was carried out in accordance with the guidelines of the Organization for Economic Cooperation and Development (OECD, 2001).

2. Materials and methods

2.1. Material

2.1.1. Plant material

Nature of plant material

The leaves of *Annona senegalensis (Annonaceae)* and *Hallea ledermannii (Rubiaceae)* were obtained from Bouaflé (central town, Côte d'Ivoire) and Yopougon (northern suburb of Abidjan, Côte d'Ivoire) respectively, and were identified and authenticated at the Centre National Floristique (CNF) of the Université Félix Houphouët-Boigny by Professor Aké-Assi. Samples of these plants are preserved respectively under herbarium numbers 9809 Lamto 06/12/1967 and 538 Forêt du banco 14/10/1954 at this center.

Preparation of aqueous extracts

Three hundred (300) grams of dried *Annona senegalensis* or *Hallea ledermannii* leaves, cut into pieces, are boiled for 1 hour in 1.5 liters of distilled water. The resulting decoctate, filtered several times through absorbent cotton, is oven-dried at 60°C. The aqueous extraction method was used to obtain the powders used in the experiments.

2.1.2. Animal material

The experiments were carried out on healthy male rats of the species Rattus norvegicus of the Wistar strain, with a body weight of between 200 and 250g. The rats were reared at the UFR

Biosciences animal house of the Université Félix Houphouët-Boigny at room temperature (25°C). Animals had access to water and food (pellets) ad libitum. Animals were treated in accordance with ethical rules concerning the use of laboratory animals.

2.2. Methods

2.2.1. Diabetes induction

For diabetes induction, seven (7) batches of five (5) male rats weighing between 200 and 250 g were formed. After measuring their basal blood glucose, they were given a single intraperitoneal dose of alloxane (75 mg/kg bw), diluted in 0.9% physiological sodium chloride solution. Rats with permanent hyperglycemia between 158 and 238 mg/dl were considered diabetic (Ndomou, 2014) (Table I).

Table 1 Blood glucose values in rats, before and after induction of diabetes

Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7
Basal fasting blood glucose before diabetes induction (mg/dl)						
70 ± 12	79.5 ± 2.5	82.5 ± 15.1	87 ± 11	81 ± 18	80.5 ± 3.5	84 ± 14
Fasting blood glucose after 72 hours of diabetes induction (mg/dl)						
283 ±103.3	265.5 ±56.01	170 ±41.46	418.8 ±84.19	179.5 ±40.83	398 ± 71	212.8 ± 76.07

2.2.2. Treatment of diabetic rats

Test substances such as aqueous plant extracts or the reference product glibenclamide or distilled water were administered to diabetic rats on a daily basis over a period of four (4) and thirteen (13) weeks. To assess the protective effects of these substances on the liver and pancreas of these rats, treatment was as follows:

- -Batch 1, non-diabetic control rats: these rats received daily by gavage two (2) ml of distilled water;
- Batch 2, untreated diabetics: these rats received daily by gavage two (2) ml of distilled water;
- Batch 3, diabetics: these rats received daily by gavage two (2) ml of Glibenclamide solution dosed at 10-2 mg/kg bw (Gli10);
- Batch 4, Diabetic: these rats received daily by gavage two (2) ml of *Annona senegalensis* aqueous extract dosed at 100 mg/kg bw (EAAs100);
- Batch 5, Diabetic: rats given daily by gavage two (2) ml of the aqueous extract of *Annona senegalensis* dosed at 200 mg/kg bw (EAAs200);
- Lot 6, Diabetic: these rats received daily by gavage two (2) ml of the aqueous extract *Hallea ledermannii* dosed at 200 mg/kg bw (EAHl200);
- Lot 7, Diabetic: these rats received daily by mouth, 2 ml of the aqueous extract *Hallea ledermannii* dosed at 400 mg/kg bw (EAHl400).

2.3. Pancreas dissection of diabetic rats

Maximum fasting blood glucose value after two measurements: 126 (mg/dl)

After four (4) and thirteen (13) weeks of treatment, some diabetic rats were sacrificed by decapitation following ethyl urethane anaesthesia (Ndomou, 2014). Dissection of the pancreas of these rats was performed and used to determine their relative weight, followed by histological analysis.

2.3. Calculation of relative organ weight

The weight of the liver and pancreas was expressed as a percentage of the animal's live weight obtained during the last weighing. Relative organ weight is determined according to the following formula:

$$\text{Relative weight of organ} = \frac{\text{Organ weight}}{\text{Animal body weight}} \times 100\ (\%)$$

2.3.1. Histological techniques

The aim of vital organ histology is to reveal any microscopic toxic effects of aqueous extracts of *Annona senegalensis* and *Hallea ledermenii*. All the techniques used were in accordance with those in use at the anatomy-pathology laboratory of the Unité de Formation et de la Recherche (UFR) des Sciences Médicales of the Université Felix Houphouët-Boigny. These techniques involve several steps:

fixation of the rat kidney in 10% formalin; dehydration with alcohol and thinning of the kidney in three successive toluene baths; impregnation in two liquid kerosene baths in an oven; embedding of the kidney in kerosene; 5 pm sections of the kidney using a microtome; dewaxing of kidney sections in the oven; staining of kidney sections in a hemathein bath; mounting of coverslips on the slide; observation and measurement of histological sections of the kidney (Hould, 1984).

2.4. Statistical analysis

Graph Pad Prism 5 software (San Diego, California, USA) was used for statistical analysis of values and graphical representation of data. Statistical differences between results were determined by analysis of variance (ANOVA), followed by the Tukey-Kramer multiple comparison test, with a significance threshold of $p < 0.05$.

3. Results

3.1. Analysis of relative liver and pancreas weights of diabetic rats after four (4) and thirteen (13) weeks of treatment.

The relative weight of the liver of diabetic rats was calculated after four (4) weeks, while that of the pancreas of these animals was calculated after four (4) and thirteen (13) weeks of experimentation (Tables II and III). After these two treatment periods, it was found that the relative weight of these organs did not change significantly in all test animals, compared with that of non-diabetic rats.

Table 2 Effects of aqueous extracts of *Hallea ledermannii* on relative liver weight in diabetic rats after 4 weeks of treatment

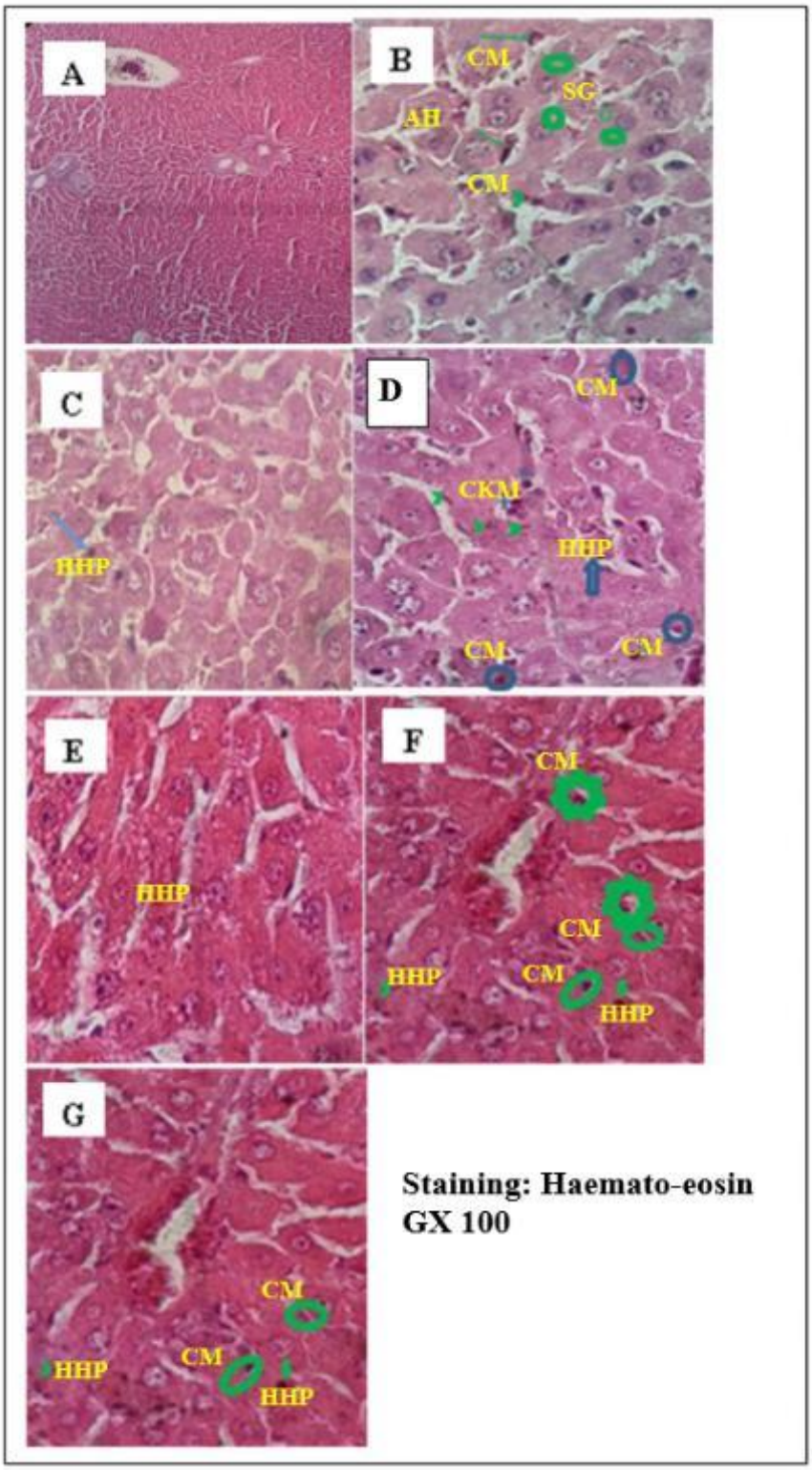
Batch 1	**Relative liver weight (%) after 4 weeks of treatment**
Normal Controls	2.21 ± 0.21
Diabetic Controls	2.17 ± 0.01
Glib 10 (10 mg/kg bw)	2.83 ± 0.08
EAAs 100 (100 mg/kg bw)	2.19 ± 0.04
EAAs 200 (200 mg/kg bw)	2.54 ± 0.03
EAHl 200 (200 mg/kg bw)	2.51 ± 0.22
EAHl 400 (400 mg/kg bw)	2.74 ± 0.39

Results are presented as mean ± SEM, n = 5; $p > 0.05$ compared to untreated or normal diabetic controls

Table 3 Influence of extracts of *Annona senegalensis* and *Hallea ledermannii* on the relative weight of the pancreas in rats after 4 and 13 weeks of treatment

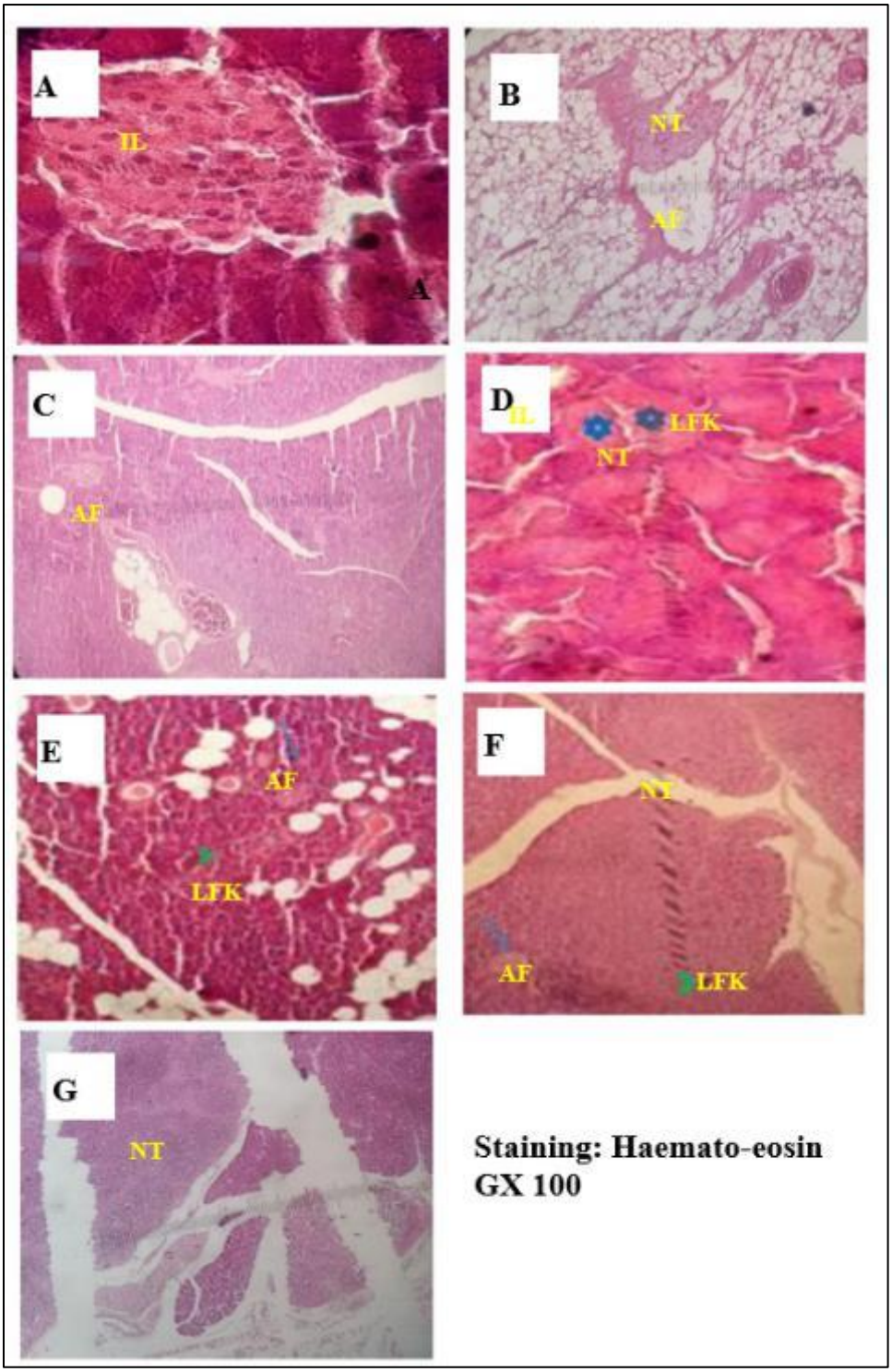
	Relative weight of the pancreas (%)	
	4 weeks of treatment	13 weeks of treatment
Normal Controls	0.39 ± 0.08	0.42 ± 0.09
Diabetic Controls	0.24 ± 0.01	0.35 ± 0.03
Glib 10 (10 mg/kg bw)	0.30 ± 0.01	0.25 ± 0.01
EAAs 100 (100 mg/kg bw)	0.26 ± 0.01	0.24 ± 0.01
EAAs 200 (200 mg/kg bw)	0.29 ± 0.01	0.25 ± 0.03
EAHl 200 (200 mg/kg bw)	0.37 ± 0.04	0.26 ± 0.05
EAHl 400 (400 mg/kg bw)	0.27 ± 0.04	0.25 ± 0.01

3.2. Histological analysis of the effects of the extracts on the liver and pancreas after four (4) and thirteen (13) weeks of treatment.



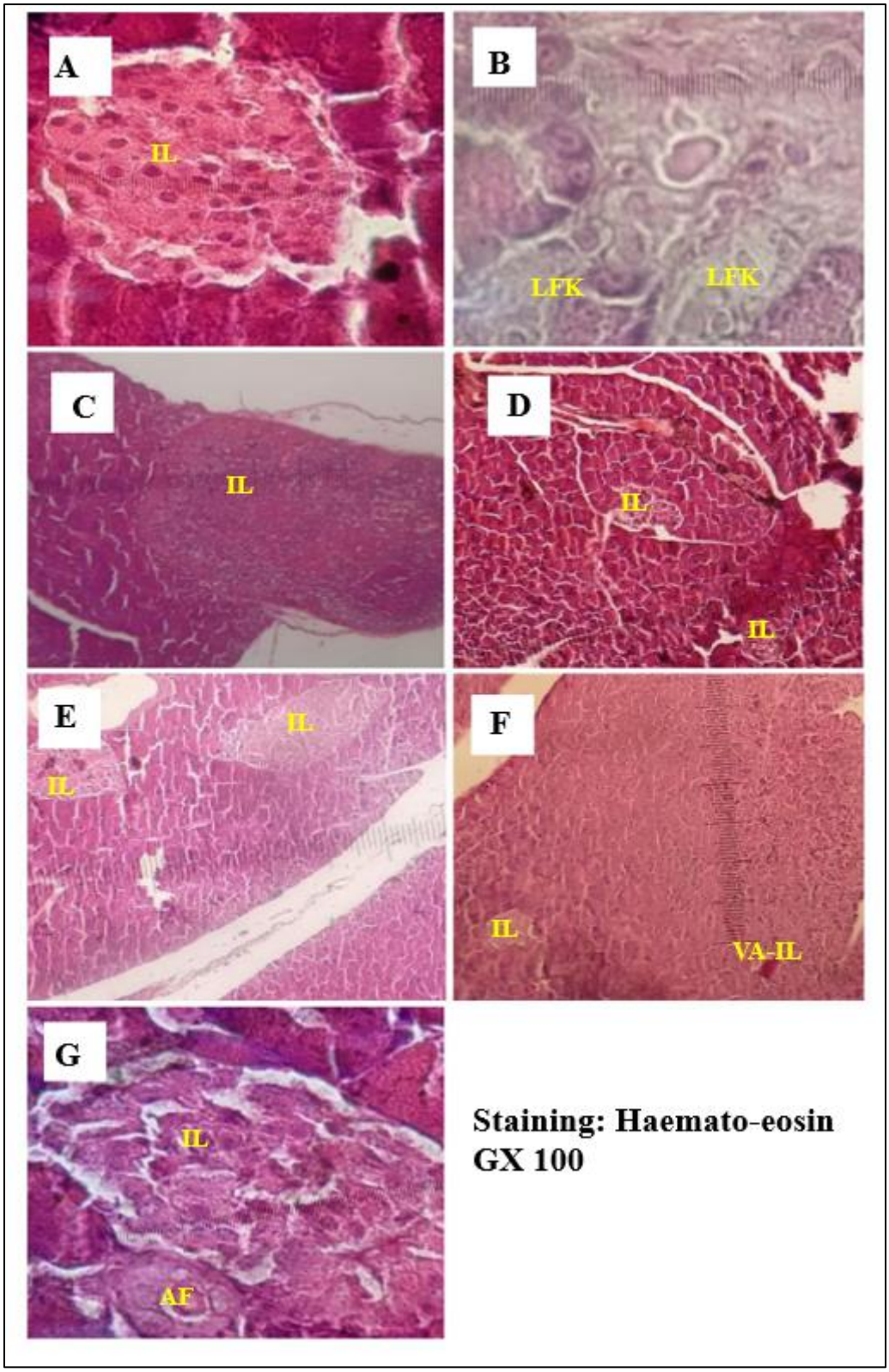
Non-diabetic controls (A); Untreated diabetic controls (B); Diabetic rats treated with Gli10 (C); EAAS100 (D); EAAs200 (E); EAHl200 (F) and EAHl400 (G).EAAS: Aqueous extract of *Annona senegalensis* (100 and 200 mg/kg bw); EAHl: Aqueous extract of *Hallea ledermannii* (200 and 400 mg/kg bw); Gli: Glibenclamide (10 mg/kg bw);SG: Glycogenic supplement; CK: Kpuffer cell; M: Myelinosome; P: Peroxisome; CM: Mallory's body; AH: Hepatocyte apoptosis; HH: Hypertrophied hepatocytes.

Figure 1 Microphotographs of liver sections in diabetic rats after 28 days of treatment.



Non-diabetic controls **(A);** Untreated diabetic controls **(B);** Glib10 treated diabetic rats**(C);** EAAS100 **(D);** EAAs200 **(E);** EAHl200 **(F)** and EAHl400 **(G).EAAS:** Extrait aqueux de *Annona senegalensis* (100 et 200 mg/kg pc); **EAHl**: Aqueousextract of *Hallea ledermannii* (200 and 400 mg/kg bw); **Gli** (10 mg/kg bw): Glibenclamide;**IL**: Islets of Langerhans; **LFK**: Fibrocystic lesions; **AF:** Focal apoptosis; **VA-IL:** Apoptotic remnant of Islets of Langerhans

Figure 2 Microphotographs of pancreas sections in diabetic rats after 28 days of treatment.



Non-diabetic controls **(A);** Untreated diabetic controls **(B);** Glib10-treated diabetic rats(C); EAAS100 **(D);** EAAs200 (E); EAHl200 (F) and EAHl400 **(G)**.**EAAS:** Aqueous extract of *Annona senegalensis* (100 and 200 mg/kg bw); **EAHl**:Aqueous extract of *Hallea ledermannii* (200 and 400 mg/kg bw); Gli (10^{-2} mg/kg bw):Glibenclamide; IL: Islets of Langerhans; LFK: Fibrocystic lesions; **AF:** Focal apoptosis;**VA-IL**: Apoptotic remnant of Islets of Langerhans.

Figure 3 Microphotographs of pancreas sections in diabetic rats, after 91 days of treatment.

Histological sections of the liver were analyzed after four (4) weeks of treatment, while those of the pancreas were analyzed after four (4) and thirteen (13) weeks of experimentation, as shown in Figure 1, Figure 2 and Figure 3 respectively. Analysis of liver histological sections after four (4) weeks of treatment revealed several abnormalities in all diabetics, compared with non-diabetic rats. The liver sections of untreated animals showed Kupffer cells containing myelinosomes (Figure 1B). Rats treated with glibenclamide (Gli10), aqueous extracts of *Annona senegalensis* (EAAs100 and 200 mg /kg bw) and *Hallea ledermannii* (EAHl 200 and 400 mg /kg bw) showed highly hyperplastic hepatocytes with numerous peroxisomes in the cytoplasm (Figures 1C, D, E, F and G). Particularly in animals treated with EAAs200 and EAHL400, Mallory's body was present in their liver section (Figures 1E and G).

During the four (4)-week treatment period, histological analysis of the pancreas of test rats showed that the islets of Langerhans of all diabetic rats treated with the substances (Gli10; EAAs100; EAAs200; EAHl 200 and EAHl 400) or not treated (Figure 2B) were necrotic and affected by apoptosis, compared with those of non-diabetic rats (Figure 2A). In addition, severe lymphocytic chronic pancreatitis was observed in this vital organ of both treated and untreated diabetic animals. After thirteen (13) weeks of treatment, histological sections of the pancreas were taken. Microscopic observation revealed the destruction of the islets of Langerhans in the pancreas of untreated diabetic rats, giving way to fibrotic lesions (Figure 3B). In animals treated with glibenclamide (Figure 3C) and *Annona senegalensis* extracts (EAAs100 and EAAs200) (Figures 3 D and E), these sections showed a normal pancreas with islet regeneration, compared with those from normal rats. Rats treated with *Hallea ledermannii* extracts (EAHl 200 and EAHl 400) showed discrete islet regeneration in histological sections, with apoptotic remnants of islets (Figure 3F) and focal apoptosis of an exocrine pancreas cell (Figure 3G).

4. Discussion

Relative weight change and histological analysis of liver and pancreas were taken into account to verify the safety of aqueous extracts of *Annona senegalensis* (EAAs) and *Hallea ledermannii*

(EAHl). The effects of EAAs and EAHl on relative liver and pancreas weights at D28 and D91 showed no significant change ($p > 0.05$) in diabetic rats (treated or untreated) compared with the non-diabetic control.

The histological study of the liver was performed after four (4) weeks of treatment, while that of the pancreas was performed after four (4) and thirteen (13) weeks of experimentation. Analysis of histological sections of the liver after four (4) weeks of treatment revealed several

abnormalities in all diabetic rats, compared with non-diabetic rats. Indeed, the liver sections of untreated diabetic animals showed Kupffer cells containing myelinosomes. A similar study showed that diabetes induced liver damage in diabetic animals, which exhibited swollen degeneration, mild portal inflammation and interface hepatitis (Abdelrazek et al., 2018). In another study, histological evaluation also showed dilatation and congestion of the central and portal veins (Taghizadeh et al., 2018).

Liver sectioning of rats treated with glibenclamide (Gli10), EAAs (100 and 200 mg /kg bw) and EAHl (200 and 400 mg /kg bw) revealed highly hyperplastic Hepatocytes with numerous peroxisomes in the cytoplasm associated with dilation and proliferation of the rough endoplasmic reticulum. These observations are contrary to studies carried out which have shown that saffron can effectively control glycemia in the alloxane-induced diabetes model in rats without liver and kidney toxicities (Kianbakht et al., 2011). Our study also stands in contrast to another which demonstrated that a one-month treatment with saffron at a dose of 40 mg/kg/day resulted in a significant reduction in oxymetholone-induced hepatic and renal degenerative changes (Kheirandish et al., 2021). These highly significant abnormalities are indicative of increased hepatocyte activity, which leads to the destruction of liver tissue (Mohamed et al., 2016).

After 28 days of treatment, analysis of histological sections of the pancreas of test rats showed that the islets of Langerhans of diabetic rats (treated or untreated) were necrotic and destroyed compared with those of non-diabetic rats.

In rats made diabetic by injection of streptozotocin, structural restoration of pancreatic islets was observed (Kanter et al., (2007); Sheikh et al., (2012) El-Ameen et al., (2015)). These results are similar to those of other researchers (Baluchenjadmojard et al., 2003). These authors showed the regenerative and protective effect of aqueous garlic extract (Allium sativum (Amaryllidaceae)) on the islets of Langerhans of treated diabetic rats. This islet-regenerating effect observed in our study could be due to the presence in our plant extracts of anti-diabetic chemical compounds such as flavonoids, saponosides, polyterpenes and tannins, which influence pancreatic P cells and stimulate insulin secretion through their ant-ioxidant activities (West, (2000); Sarkhail et al., (2007)).

5. Conclusion

This study analyzed the relative weight of the liver and pancreas of rats made diabetic by alloxane induction. Histological analyses of these organs were also carried out after four (4) to thirteen (13) weeks of phytotherapy.

For the analysis of the relative weight of the liver and pancreas of diabetic rats, it should be noted that this parameter did not vary significantly in these organs of these animals. Concerning the histological study of the liver and pancreas of test rats, four (4) weeks after treatment, these organs were intoxicated by alloxane. After thirteen (13) weeks of treatment with our plants (aqueous extracts of *Annona senegalensis* (EAAs) and *Hallea ledermannii* (EAHl)), the liver and pancreas were regenerated. This study highlighted the hepatoprotective properties and pancreatic regenerative activities of EAAs and EAHl in diabetic rats. These aqueous extracts could therefore be used in traditional medicine for the treatment of diabetes.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Prior to this work, the acute toxicity test for the plants used, in Wistar rats, was carried out in accordance with the guidelines of the Organisation for Economic Co-operation and Development (OECD 423 of 2001).

Declaration of informed consent.

I and the three other authors of this manuscript have reached a clear consensus regarding the publication of this article as a research article.

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