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Protective effects of *Dioscorea alata* and *D. rotundata* extracts on liver, pancreas, and kidney in alloxan-induced diabetic guinea pigs

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ABSTRACT

Introduction

Diabetes mellitus is a chronic metabolic disease that affects a large fraction of the world's population. In addition to the many complications associated with it, the lack of effectiveness and insufficiency of current treatments have driven the WHO to return to traditional medicine, which generally involves the use of plant materials as remedies.

Purpose

This study investigates the protective effects of *Dioscorea alata* and *D. rotundata* extracts on the liver, pancreas, and kidney in alloxan-induced diabetic guinea pigs.

Methods

Diabetes was induced by a single intraperitoneal injection of alloxan (150 mg/kg). Post-induction, guinea pigs (*Cavia porcellus* L.) were treated orally with *Dioscorea alata* and *D. rotundata* extracts (200 mg/kg and 400 mg/kg, respectively) for 21 days. The liver, pancreas, and kidneys were assessed for histopathological changes. Two standard synthetic antidiabetics (insulin 5 IU/100g and glibenclamide 5 mg/kg) were used as positive controls.

Results

Histopathological examination revealed marked improvement in the tissue morphology of the liver, pancreas, and kidneys in the treated groups compared to the untreated group. The renal parenchyma showed a fairly normal structure, with the Malpighian glomerulus clearly visible, exhibiting hyperplastic cell nuclei in full regeneration.

Conclusion

Tuber extracts from these two yam species have shown potential to repair and regenerate tissue damaged by the deleterious effects of alloxan-induced free radicals and permanent hyperglycemia during diabetes. The evident antidiabetic and cytoprotective potential of these plant species could be utilized for the development of biologically active natural molecules for the treatment of diabetes mellitus and its complications. The study is limited by its short duration, and further long-term studies with varied dosage regimens are recommended to better understand the effects of these extracts. Additional research should explore the specific bioactive compounds responsible for the observed protective effects and their mechanisms of action.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by permanent hyperglycemia caused by an absolute or relative insufficiency of insulin (Melle Bennacer & Melle Cherifi, 2022; Wild et al., 2004). Defects in insulin secretion, insulin action, or both lead to elevated blood glucose levels, which cause serious metabolic disturbances (Simon, 2016; Bammoune & Babaammi, 2022). Today, the use of plants for the treatment of diseases, including diabetes mellitus, is common, offering hope to the global population. Due to the presence of secondary metabolites with pharmacological properties, herbal medicine has evolved significantly (Melle Sahli & Melle Saidi, 2016; Marles & Farnsworth, 1995). The World Health Organization (WHO) has endorsed the use of traditional medicines for disease treatment. WHO acknowledges that plant-based treatments are essential due to the financial and accessibility constraints faced by many populations when obtaining modern synthetic drugs (WHO, 2022). Additionally, due to the complications associated with diabetes mellitus and the inefficacy of current treatments, WHO has encouraged a return to traditional medicine (Bammoune & Babaammi, 2022).

Dioscorea alata and *D. rotundata*, like other yam species, have been cultivated for their starch-rich tubers since ancient times (Kerharo, 1974; Hamon, 1987). Recent studies have demonstrated the medicinal and pharmacological virtues of species in the *Dioscorea* genus, with phytochemical characterizations revealing their antioxidant effects (Lombe et al., 2023; Bukatuka et al., 2016; Kelechi et al., 2021). These species contain bioactive compounds such as phenols, flavonoids, saponins, anthocyanins, carotenoids, allantoins, and water-soluble polysaccharides (Padhan et al., 2020; Lebot et al., 2023; Zhen et al., 2023). Modern research has confirmed that yams possess pharmacological activities that improve cardiovascular health, regulate immune function, and exhibit antitumor, antibacterial, anti-inflammatory, and antidiabetic properties (Adomeniene et al., 2022; Ou-yang et al., 2018; Kundu et al., 2021). Furthermore, phytochemicals in yams, such as polysaccharides, diosgenin, polyphenols, and allantoin, have been shown to treat inflammation and metabolic disorders (Chaniad et al., 2020; Tao et al., 2018). Specifically, *Dioscorea alata* and *D. rotundata* contain significant bioactive molecules like gallic acid, epicatechin, phenolic acids, and 3'-O-Methylcaryotine (Lebot et al., 2023; Zhen et al., 2023).

In this study, histological sections of the liver, pancreas, and kidney (stained with hematoxylin-eosin H-E) from guinea pigs in the healthy control group, the untreated diabetic control group, and those treated with extracts of *Dioscorea alata* and *D. rotundata* were examined to establish a correlation between possible tissue alterations or prevention due to this treatment.

The primary aim of this research is to investigate the histological effects of hydro-methanolic extracts from the tubers of *Dioscorea alata* and *D. rotundata*, administered orally (via gavage) for 21 days at daily doses of 200 and 400 mg/kg body weight to domestic guinea pigs (*Cavia porcellus*), made diabetic by a single dose of alloxan (150 mg/kg). This research aims to promote the therapeutic importance of local food plants, particularly yams, and explore the possibility of isolating active principles from these plants as a protective agent against liver, pancreatic, and renal complications associated with diabetes.

METHODS

Plant Material

The plant material consisted of yam tubers (*Dioscorea alata* and *D. rotundata*) obtained from local markets in Kinshasa (DR Congo) in September 2020. They were identified at the Herbarium of the National Institute of Agricultural Studies and Research (INERA), located in the Department of Life Sciences, Faculty of Sciences and Technology, University of Kinshasa.

Preparation of Crude Extracts

Crude extracts were prepared following the method described by Onsiyor et al. (2019) and Kelechi et al. (2021), with slight modifications. The tubers were washed, peeled, and cut into small slices. They were then freeze-dried and ground into a fine powder. Subsequently, 180 g of powder was macerated in 1,800 ml of methanol-water solution (7:3 v/v) for 48 hours. The macerate was filtered and evaporated under vacuum at 45°C, and the concentrate was stored at 4°C until use. The dry matter yields were 15.05 ± 0.02% for *D. alata* and 13.83 ± 0.01% for *D. rotundata*.

Animal Material

Our animal material consisted of fifty (50) domestic guinea pigs (*Cavia porcellus L.*) in total, with weights ranging between 167 and 400 g. The animals were provided by the Laboratory of Zootechnics at the Faculty of Agronomy, University of Kinshasa. They were transported to the National Institute of Biomedical Research (INRB) in Kinshasa, where the research was conducted. Before the experiment, the animals were acclimatized for seven days to the climate and living conditions of the Pet Shop at INRB. They had access to water and food ad libitum.

Acute Exploratory Toxicity Test

The exploratory acute toxicity test was conducted using the method described by Etame (2017), Nnanga et al. (2020), and Belabaci (2019), with minor modifications. A single dose of 2000 mg/kg body weight was orally administered to a total of 10 guinea pigs (both male and female), compared to 5 negative controls treated with drinking water (10 mg/kg body weight). The animals were observed for seven days to note any changes in physical behaviour, toxicity, or mortality, and their weight evolution was monitored.

Induction of Diabetes

After their adaptation to the pet shop, the guinea pigs were subjected to a 16-hour fast, after which they received an intraperitoneal injection of alloxan monohydrate at a dose of 150 mg/kg body weight (Boussarie & Rival, 2017; Onsiyor et al., 2019). Any animal with a fasting glycaemic peak of 200 mg/dL or more was considered hyperglycaemic and reported as diabetic, to be included in the experiment three days after alloxan injection.

Experimental Protocol

Forty male guinea pigs (35 diabetic and 5 healthy), with a mean weight of 238.08 ± 64.18 g, were used in this experiment. The animals were divided into eight groups of five guinea pigs each. Extracts of *Dioscorea alata* and *D. rotundata* tubers, as well as glibenclamide, were administered daily by intra-gastric gavage for three consecutive weeks (21 days), whereas insulin was administered by intramuscular injection every three days after blood glucose measurement. During the three weeks of the experiment, weight evaluation was performed every three days. The different groups were as follows:

- **Group 1**: Healthy control, receiving placebo (drinking filtered water, 10 ml/kg body weight);
- **Group 2**: Diabetic control, untreated, receiving drinking water;
- **Group 3**: Diabetic animals treated with insulin (5 IU/100 g), a standard synthetic antidiabetic administered intramuscularly;
- **Group 4**: Diabetic animals treated with another standard synthetic antidiabetic, glibenclamide (5 mg/kg body weight) orally;
- **Group 5**: Diabetic subjects treated with an extract of *Dioscorea alata* at 200 mg/kg body weight (EDAL200);
- **Group 6**: Diabetic subjects treated with *Dioscorea alata* extract at 400 mg/kg body weight (EDAL400);
- **Group 7**: Diabetic subjects treated with *Dioscorea rotundata* extract at 200 mg/kg body weight (EDROT200);
- **Group 8**: Diabetic subjects treated with *Dioscorea rotundata* extract at 400 mg/kg body weight (EDROT400).

Body weight and blood sugar measurements were taken on the 22nd day, before the animals were sacrificed after 21 days of treatment.

Removal of Organs

After the last gavage on the 21st day, the animals were fasted for 16 hours and then sacrificed for organ removal for histopathological study (liver, pancreas, and kidney). The animals were placed under mild respiratory anaesthesia using chloroform, after which a median laparotomy was performed between the sternum tip and the umbilical area. The organs were immediately fixed in 10% formalin and prepared for subsequent histological analysis.

Ethical Approval and Dose Rationale

Ethical approval for the study was obtained from the Institutional Animal Care and Use Committee (IACUC) of the Life Sciences Department, Faculty of Science and Technology, University of Kinshasa, under protocol number 021/CDB/MSV/FST/UNIKIN.

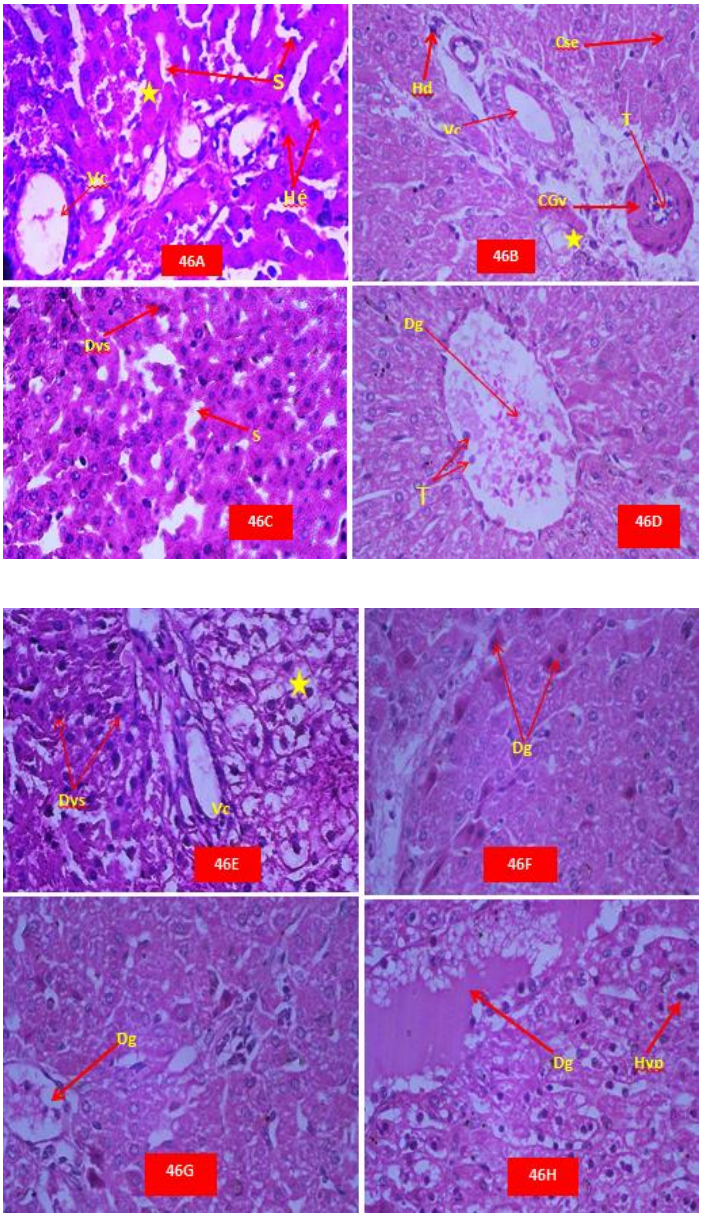
RESULTS

The experimental guinea pigs receiving a single dose of 2000 mg/kg of the hydro-methanolic extract of *Dioscorea*

alata and *D. rotundata* showed no acute toxic effects or mortality, indicating that the extract is non-toxic to the animals. The extract was also found to be hypoglycaemic, lipid-lowering, and cytoprotective at all experimental doses. All guinea pigs, except those in the diabetic control group *(Group 2)*, showed positive weight changes with weight gain in all experimental groups.

Effect of Yam Extracts on Liver Histology

Figure 1:
Liver tissue microphotographs; Haematoxylin-Eosin (H-E) staining [400x]



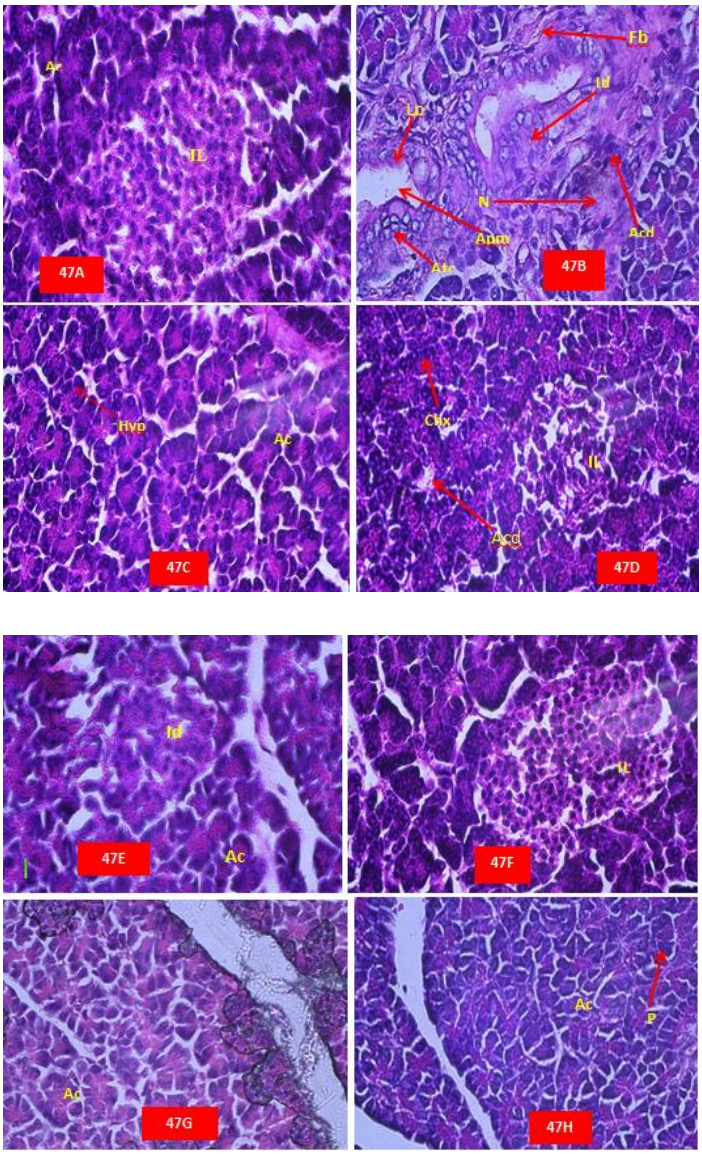
A: Negative control; B: Diabetic control; C: Insulin treated animal; D: Glibenclamide treated animal; E: animal treated with extract of *D. alata* 200mg/kg bw; F: animal treated with *D. alata* extract 400mg/kg bw; G: animal treated with *D. rotundata* extract 200mg/kg bw; H: animal treated with *D. rotundata* extract 400mg/kg bw. = Postmortem autolysis (Apm), He = Hepatocytes; Vc = Vena centrolobular; S= sinusoids, CGv= Vascular congestion, Cse=Caryolysis, Dys= Dysplasia, Dg=Degeneration of fat, T=Thrombosis, Hd= Hepatocyte degenerate, Hyp= Hyperplasia. Star indicates PMA: post mortem autolysis.

- **Negative Control Group**: Showed normal parenchymal architecture, with clearly visible and delimited central lobular veins, radiating hepatocytes with well-defined nuclei, and narrow sinusoids **(Figure 46A)**. No signs of inflammation (hepatitis) were observed, except for liquefaction autolysis due to insufficient tissue fixation.
- **Diabetic Control Group**: Showed some degenerated hepatocytes, large vascular congestion, and traces of thrombus, likely related to diabetic stress, toxic effects of alloxan, and blood circulation disorders (Charles Valla, 2003; Melle Sahli & Melle Saidi, 2016) **(Figure 46B)**. The liver tissue presented degenerative architecture, with almost invisible sinusoids and absent Remak bays.

Histopathological analysis of the livers of alloxan-induced and treated guinea pigs showed minor impairments in all treated groups **(Figures 46C, 46D, 46E, 46F, 46G, 46H)**, including caryolysis, dysplasia, and hyperplasia. Macrosteatosis was also observed, possibly due to excess fat intake by the guinea pigs (Melle Sahli & Melle Saidi, 2016), as well as thrombosis, potentially linked to alloxan and diabetic stress.

Effect of Yam Extracts on Pancreatic Histology

Figure 2:
Pancreatic tissue microphotographs; Haematoxylin-Eosin (H-E) staining [400x]



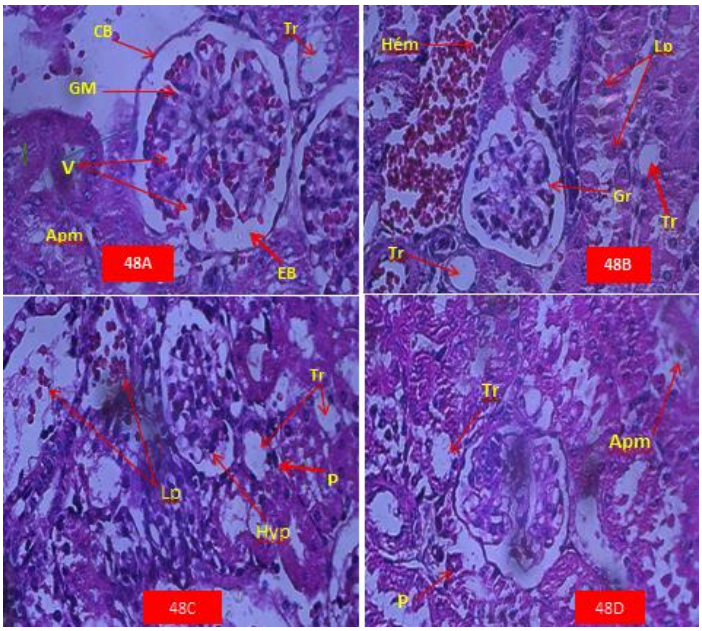
A: Negative control; B: Diabetic control; C: Insulin treated animal; D: Glibenclamide treated animal; E: animal treated with extract of *D. alata* 200mg/kg bw; F: animal treated with *D. alata* extract 400mg/kg bw; G: animal treated with *D. rotundata* extract 200mg/kg pc; H: animal treated with *D. rotundata* extract 400mg/kg pc. Ac = Acini; IL= Langerhans's island; Apm= Autolysis post-mortem; Chx= Caryorrhexis; P=Pycnosis; Fb=Fibrosis; Lp= Lipidosis; Id= disaggregated island, Hyp= hyperplasia, Acd= disaggregated Acini, Atc= Cell atrophy, N=Necrosis.

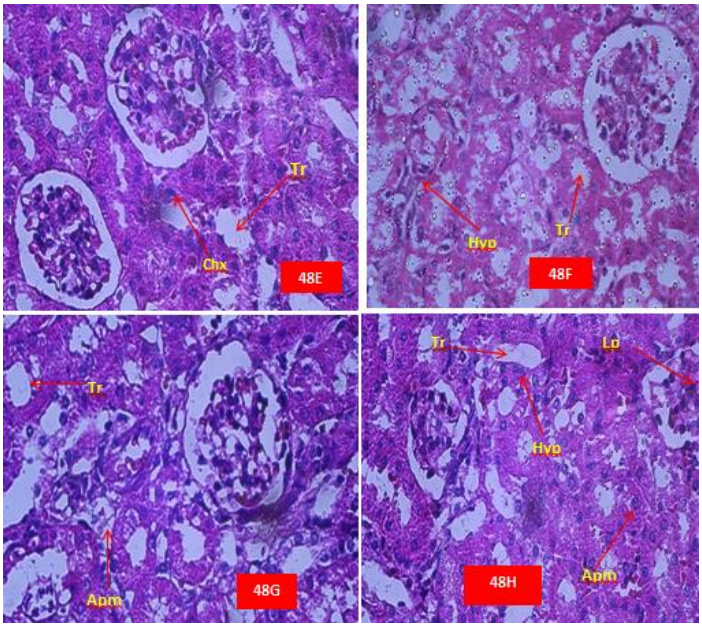
- **Negative Control Group**: Showed normal pancreatic lobular architecture, with clearly visible pancreatic acini and islets of Langerhans **(Figure 47A)**.
- **Diabetic Control Group**: Revealed significant cell modification, with tissue degeneration, fibrosis, cell necrosis, atrophy, and damaged islets of Langerhans **(Figure 47B)**.

Histopathological analysis of treated diabetic guinea pigs showed an improvement at the cellular level, with normal acini and restored islets of Langerhans, indicating the protective effects of yam extracts (Lombe et al., 2023). This protective action may be due to the antioxidant activity of the extracts, which may neutralise free radicals generated by alloxan and chronic hyperglycaemia.

Effect of Yam Extracts on Kidney Histology

Figure 3:
Microphotographs of renal tissue; Haematoxylin-Eosin (H-E) staining [400x]





A: Negative control; B: Diabetic control; C: Insulin treated animal; D: Glibenclamide treated animal; E: animal treated with extract of *D. alata* 200mg/kg bw; F: animal treated with *D. alata* extract 400mg/kg bw; G: animal treated with *D. rotundata* extract 200mg/kg pc; H: animal treated with *D. rotundata* extract 400mg/kg bw. GM = Malpighi's glomerulus; Apm = Postmortem autolysis; Hém= Hemorrhage; Lp=Lipidosis; Hyp= Hyperplasia; CB= Bowman's capsule; EB= Bowman's space; Tr= Renal tube, V= Glomerular vacuole, Gr= Narrowed glomerulus.

- **Negative Control Group**: Showed healthy cortical and medullary renal parenchyma, normal Bowman capsules, and Malpighi glomeruli **(Figure 48A)**.
- **Diabetic Control Group**: Showed significant degeneration of the renal parenchyma, with glomerular narrowing, haemorrhages, and lipidosis **(Figure 48B)**.

Treated diabetic guinea pigs showed restored renal parenchyma and glomeruli, despite minor reversible lesions such as lipidosis and pycnosis, due to pathophysiological requirements (Mayola, 2011).

DISCUSSION

Dioscoreaceae have been shown to possess anti-radical and anti-hyperglycemic properties, as previously reported by Lombe et al. (2023), Kelechi et al. (2021), and Bukatuka et al. (2016). In this histopathological study of diabetes mellitus, we aimed to highlight the effects of hydro-methanolic extracts from the tubers of local yam species *Dioscorea alata* and *D. rotundata* on an animal model relevant to humans, the domestic guinea pig (*Cavia porcellus L*), which was made diabetic through alloxan injection. This study contributes to the growing database for the therapeutic management of diabetes.

Hyperglycemia is a major factor in generating free radicals, which can exhaust antioxidant defenses, interrupt cellular functions, and cause oxidative damage to membranes (Yaribeygi et al., 2019). Organ structures and functions may be disrupted during uncontrolled hyperglycemia (Halliwed & Gutteridge, 2015). In this experimental model, alloxan exhibited cytotoxic effects on various tissues, including the liver, pancreas, and kidney (Nermeen et al., 2010; Hashemnia et al., 2012).

The pathological changes observed in the pancreatic **(Figure 1)** and renal **(Figure 2)** tissues of diabetic guinea pigs could be attributed to small inflammations and infiltrations in the kidney and liver due to the effects of alloxan (Nermeen et al., 2010; Hashemnia et al., 2012) and hyperglycemia-induced oxidative stress (Yaribeygi et al., 2019).

Effect of Treatment on Liver Histology

The liver plays a crucial role in managing blood glucose homeostasis, being the site of glycogenogenesis and glycogenolysis under the influence of insulin and pancreatic glucagon (Bamagous et al., 2018). Diabetic guinea pigs demonstrated liver damage marked by degenerated hepatocytes, congestion of the central veins, caryolysis, and thrombosis, compared to healthy control animals. These degenerative effects on hepatocytes can be attributed to the diabetogenic action of alloxan, as reported by Abd El Latif et al. (2014) in alloxan-induced diabetic rats. However, in the treated animals, signs of hepatocyte replacement hyperplasia and liver cell regeneration were visible, likely due to the restorative effects of *D. alata* and *D. rotundata* extracts during the 21-day observation period.

The observed liquefaction autolysis in animals undergoing treatment could be attributed to insufficient dehydration during organ fixation in formalin and/or issues during the alcohol dehydration series. This might also point to under-dosed or ineffective formalin or alcohol baths.

Effect on Pancreatic Histology

The pancreas is particularly vulnerable to free radical damage induced by alloxan, which can lead to various

alterations, including the atrophy of islets of Langerhans, a reduction and destruction of β cells, and degeneration of pancreatic acini (Fuman, 2015; Kelechi et al., 2021). In contrast, healthy guinea pigs in the negative control group exhibited intact pancreatic tissues with regular acini and islets, showing a normal lobular architecture. The pancreatic tissues of alloxan-inoculated guinea pigs, despite some repair by plant extracts in treated groups, still showed degenerative traces of atrophied β cells and damaged islets, likely resulting from alloxan's toxic effects. Similar findings were observed by Bouhouche (2014) in Wistar rats treated with 150 mg/kg of alloxan, where alloxan, an analogue of toxic glucose, accumulates in β cells, leading to their destruction. Higher doses of alloxan (200-250 mg/kg) have been reported to cause significant cytoplasmic and nuclear necrosis (Bouhouche, 2014). The protective effects of *D. alata* and *D. rotundata* likely contributed to the regeneration of pancreatic cells against free radicals. Pancreatic cells are stable and capable of regeneration after damage, with surviving cells proliferating to compensate for lost cells (Spinas, 1999, as cited by Bammoune & Babaammi, 2022).

Effect on Kidney Histology

The kidneys are primary targets of diabetes, and hyperglycemia often affects the function of small blood vessels and kidney tissues, leading to impaired renal filtration (nephron function) and diabetic nephropathy (El-Bouhi et al., 2018). This major renal complication of diabetes can evolve into chronic kidney disease, potentially resulting in long-term renal failure (El-Bouhi et al., 2018). The evaluation of renal tissues in animals receiving 150 mg/kg of alloxan revealed degenerative changes, including hemorrhages, pycnotic cell nuclei, and fat degeneration, particularly in diabetic control subjects. These degenerative changes are likely related to diabetes pathogenesis, caused by oxidative stress-induced free radicals and protein glycosylation, which disorganizes tissues (Đurašević et al., 2019). Negative control animals showed healthy renal cortical parenchyma with well-organized glomeruli and tubules.

Mayola (2011) reported that cells under increased physiological or pathological demand attempt to adapt to maintain cellular and tissue homeostasis. This adaptation may involve hypertrophy, atrophy, hyperplasia, or dysplasia, which can lead to reversible (non-fatal) or irreversible (fatal) injuries. The substitution and regenerative hyperplasia observed in guinea pigs suggest tissue protection and repair, as evidenced by the presence of young developing nuclei within normal parenchyma, similar to those found in healthy animals in the negative control group.

This study has shown that extracts from these plants can prevent liver, pancreatic, and kidney deterioration in diabetic states. The protective effects of *D. alata* and *D. rotundata* on these organs in diabetic models may be attributed to various phytochemicals. Saponins, known for their antioxidant properties, neutralize free radicals and reduce oxidative stress, thereby protecting organ tissues (Li et al., 2020). Flavonoids, such as quercetin and kaempferol, reduce inflammation and improve insulin sensitivity, supporting pancreatic and liver function (Kumar et al., 2021). Alkaloids, notably diosgenin, modulate metabolic pathways in diabetes by enhancing insulin secretion and sensitivity while protecting tissues from inflammation and oxidative stress (Tiwari, 2018). Polyphenols also exert antioxidant and anti-inflammatory effects, inhibiting pro-inflammatory cytokines and supporting antioxidant defenses (Nicolle, 2022). These phytochemicals act synergistically to enhance organ function and reduce diabetic complications.

Limitations

This study has several limitations. Firstly, the use of a single animal model limits the generalizability of findings to other species or humans. Additionally, variability in the composition of *Dioscorea* extracts may affect result consistency. The relatively short duration of the study also does not account for long-term effects or potential side effects of prolonged use. These factors should be considered when interpreting the findings and setting realistic expectations for the protective effects of *Dioscorea* extracts.

Future studies should include clinical trials to validate these findings in humans. In-depth research is needed to elucidate the molecular mechanisms through which these phytochemicals exert their effects, including their interactions with specific metabolic and signaling pathways. Moreover, standardizing extract composition

and assessing the long-term safety and efficacy of *Dioscorea* extracts will be essential for translating these findings into practical therapeutic applications.

CONCLUSION

The study demonstrated that the hydro-methanolic extracts of *Dioscorea alata* and *D. rotundata* tubers have significant hypoglycemic, lipid-lowering, and cytoprotective effects in alloxan-induced diabetic guinea pigs. The yam extracts exhibited protective properties against the oxidative damage caused by hyperglycemia, particularly in the liver, pancreas, and kidneys. These findings support the potential use of these local yam species as complementary therapies in the management of diabetes and its complications. Further research is required to better understand the mechanisms behind the protective effects of these yam tuber extracts and to explore their potential applications in human diabetes management.

Ethics Approval: Ethical approval for the study was obtained from the Institutional Animal Care and Use Committee (IACUC) of the Life Sciences Department, Faculty of Science and Technology, University of Kinshasa, under protocol number 021/CDB/MSV/FST/UNIKIN.

Conflicts of Interest: None declared.

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