ejpmr, 2023, 10(2), 352-360

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

ISOLATION, STRUCTURAL DETERMINATION AND ANTI-HYPERGLYCEMIC EFFECT OF DIETHYL TEREPHTHALATE EXTRACTED FROM THE LEAVES OF *DIALIUM GUINEENSE* (*CAESALPINIACEAE*)

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Article Received on 22/12/2022 **Article Revised on 12/01/2023** **Article Accepted on 01/02/2023**

ABSTRACT

Previous work had demonstrated the lack of hypoglycemic effect of the butanol-ethyl acetate fraction (BEAF) of the leaves of *Dialium Guineense* (*Caesalpiniaceae*). However, this same fraction is anti-hyperglycemic in glucose tolerance test in type 2 diabetic rats. The purpose of that study was to evaluate the effect on blood glucose of dietyl terephthalate (DT) isolated from BEAF of *D. guineense* leaves. Diethyl terephthalate (DT) was tested in normoglycemic rats, glucose tolerance test and type 2 diabetic rats. *Per os* administration of DT in normoglycemic rats is not associated with a significant change in basic blood glucose. At 30 mg/kg *per os*, blood glucose ranges from 0.76±0.02 to 0.84±0.02 g/L (ns, n=5). Under the same conditions, similar results were observed at 100 mg/kg *per os* (0.91±0.04 vs 0.95±0.03 g/L) (ns, n=5). In glucose tolerance test, prior administration of DT (30 mg/kg, 100 mg/kg, *per os*) significantly prevents the appearance of frank hyperglycemia. The blood glucose was 1.10±0.04 g/L and 1.29±0.08 g/L, respectively at 30 mg/kg and 100 mg/kg *per os*, after DT administration vs 2.04±0.13 g/L in control group ($p<0.05$, n=5). The daily administration of DT (30 mg/kg, per os) in type 2 diabetic rats significantly prevents the hyperglycemia previously observed in the control group. The effect profile on blood glucose of DT is identical to that butanol-ethyl acetate fraction (BEAF) of the leaves of *D. guineense* and is reminiscent that of antihyperglycemic agents of thiazolidine-dione group. The anti-hyperglycemic action of DT would involve the body peripheral tissues.

KEYWORDS: *Dialium guineense*, Leaves, Blood glucose, Diethyl terephthalate.

1. INTRODUCTION

Type 2 diabetes results from resistance of peripheral tissues to the action of insulin, associated with disorders of insulin secretion. Insulin resistance results from a decrease in the sensitivity of peripheral tissues to the action of insulin. In fact, the mechanisms involved in insulin resistance are an insensitivity of the insulin receptor and a decrease in the expression of GLUT-4 glucose transporter at the plasma membrane of skeletal striated muscle cells.[1,2] The body compensatory response to insulin resistance is an insulin hypersecretion from the β-pancreatic cells of the Langherans ileum.[3] Compensatory insulin hypersecretion leads to the long run to depletion of β-pancreatic cells and insulin secretion disorders.

The treatment of type 2 diabetes uses insulin secretors such as sulfonylureas, whose leader is glibenclamide and more recently GLP-1 (glucose-like peptide-1) analogues (exenatide, liraglutide) and DDP-4 (dipeptidyl-peptidase-4) inhibitors (vildagliptin, saxagliptin).[4-6] It also involves molecules that improve the sensitivity of peripheral tissues to the action of insulin, namely biguanides such as metformin and thiazolidines-diones like rosiglitazone and pioglitazone.[7-11]

Natural products, especially those of plant origin, have always been an important source of molecules of therapeutic interest. Indeed, many of the drugs in the therapeutic arsenal have natural or hemiisynthetic origin, most often from a molecule of the plant kingdom. According to the World Health Organization (WHO), 80% of people in developing countries have used medicinal plants for their primary health care at least once in their lives.[12]

Dialium guineense (*Caesalpiniaceae*) is a plant of the traditional senegalese pharmacopoeia commonly known

as "*Solom*" in wolof. In traditional environments, *D. guineense* is used as an antidiabetic, antipyretic and defatigant.[13]

Phytochemically, a previous study had revealed the presence of alkaloids, anthraquinones, flavonoids, saponins and tannins in *D. guineense* leaves.[14]

The aqueous or methanol extract of *D. guineense* leaves, containing tannins and flavonoids, doesn't have any hypoglycemic effect on normoglycemic rats in acute administration. Howhever, it is antihyperglycemic in glucose tolerance test and after daily administration in type 2 diabetic rats. Moreover, the F5 fraction of the methanol extract of *D. guineense* leaves containing essentially flavonoids is both hypoglycemic in normoglycemic rats and anti-hyperglycemic in glucose tolerance test.[15,16]

The butanol-ethyl acetate (BEAF) fraction of *D. guineense* leaves containing flavonoids and tannins has no effect on blood glucose in normoglycemic rats. However, it is anti-hyperglycemic in glucose tolerance test and type 2 diabetic rats.[17]

The purpose of that study was to isolate, identify and evaluate the effect on blood glucose of BEAF compounds of *D. guineense* (*Caesalpiniaceae*) leaves.

2. MATERIALS AND METHODS

2.1 Plant material

Fresh leaves of *D. guineense* were harvested in Cabrousse in the region of Ziguinchor in Senegal, in December 2018. They were identified at the Botanical Laboratory of the Faculty of Medicine, Pharmacy and Odontology (FMPO) of Cheikh Anta Diop University (CADU) and then dried at the Laboratory of Pharmacology of said Faculty. After being dried in the shade for two weeks at room temperature (25°C), the leaves were pulverized using a Brabender® electric crusher. The powder obtained is of bitter taste and green colour. It has a sternutatory power.

2.2 Animal Material

It is made up of normoglycemic rats of the *Wistar Kyoto* strain, bred at the Laboratory of Pharmacology pet store at 25°C, under the light of the day and darkness at night. They were fed with Poulette at SENTENAC®'s mill from Dakar and had free access to tap water.

2.3 EXPERIMENTAL PROCEDURES

2.3.1 Preparation of Butanol-Ethyl acetate fraction (BEAF)

The powder of *D. guineense* leaves (300 g) has been subjected to an aqueous decoction for 1h 30 min. After cooling and filtration, the aqueous filtrate was subjected to a liquid-liquid separation in a separating funnel, successively with ethyl acetate and n-butanol. The collected filtrates were mixed and gave an butanol-ethyl acetate fraction (BEAF) after evaporation. The diagram in Fig. 1 describes the BEAF extraction diagram.[17]

2.3.2 Purification of Butanol-Ethyl acetate fraction (BEAF)

The purification was performed on a glass TLC plate covered with silica gel, coated with the fluorescent indicator F254. BEAF has been dissolved in methanol. Using capillaries, spots were applied to the ends of the 20x20 cm *silica* gel TLC plate about 1cm from the edge on one side. After drying the stains, the plates were placed into a saturated development vessel with an ethanol/ethyl acetate/chloroform solvent eluent system (5/2.5/2.5). When the front of the solvent covered three-quarters of the plate, it was removed and the front of the solvent was immediately marked. The plate was dried at room temperature. It was then analysed using a UV lamp. The distances travelled by each point were measured using a ruler and recorded. The stains have been carefully scraped, separately dissolved in methanol and centrifuged for 20 min. The supernatants were concentrated and allowed to evaporate at room temperature. The partially purified compounds obtained were stored in pillboxes and put in a desiccator. This process was repeated eleven times in a row for each used plate. A total of 5 spot groupings were obtained. A distinction is made between HD2-R1, HD2-R2, HD2-R3, HD2-R4, HD2-R5, with respective frontal rapports (fr) fr ratios (HD2-R1) = 0.25; fr (HD2-R2) = 0.33; fr (HD2-R3) = 0.55; fr (HD2-R4) = 0.72 and fr (HD2-R5) = 0.88 (Table 1). HD2-R1 mass m (HD2-R1) product equals to 148 mg was characterized by NMR (1D and 2D).

2.3.3 NMR Spectroscopy

2.3.3.1 13C NMR spectrum of HD2-R1 compound

The analysis of the 13C NMR spectrum (Fig. 2a-b) reveals the presence of 12 carbons:

- 2 carbonyls C1 and C2 at 169.2 ppm corresponding to an ester
- 6 aromatic carbons among which 2 quaternary C3 and C4 at 133.5 ppm and 4 CH C5, C6, C7, and C8 at 129.8 ppm,
- 2 methylene carbons C9 and C10 at 62.8 ppm,
- 2 methyl carbons C11 and C12 at 14.3 ppm.

2.3.3.2 1H NMR and HSQC spectrum

The combined analysis of the HSQC spectra (Fig. 3) and the 1H NMR (Fig. 4) assigned each proton to the carbon to which it is directly related. On NMR 1H spectrum we distinguish:

- A doublet (d) at 7.6 ppm corresponding to the aromatic protons H5, H6, H7, H8.
- A 4.3 ppm quadriplet (q) corresponding to H9 and H10 methylenes.
- A triplet (t) at 1.3 ppm corresponding to the methyl protons H11, H12.

2.3.3.3 COSY spectrum of HD2-R1 compound

The COSY spectrum (Fig. 5a-b-c) shows two couplings. Protons H9 and H11 couple in ^{3}J as well as protons H10

and H12. The aromatic protons H6 and H8, as well as the protons H5 and H7 couple in ^{3}J. These fragments were used to position C5, C6, C7, C8, C9, C10, C11, C12.

2.3.3.4 HD2-R1 Compound HMBC Spectrum
The HMBC spectrum (Figure 6a-b) allows to visualize heteronuclear couplings in 3J, 4J. Thus, based on the analysis of the HMBC spectrum of this compound, the position of C9 and C10 is confirmed by the correlation of their protons with C1 and C2 carbonyls. Thus, C11 and C12 are assigned. Quaternary aromatic carbons C3 and C4 are positioned thanks to their correlations with protons H5 and H6. Chemical movements are recorded in Table 2.

2.3.4 Pharmacological Trials
The use of animal material has been approved by the ethics committee of Cheikh Anta DIOP University (CADU) of Dakar (Protocol: 0373/2019/CER/UCAD).

2.3.4.1 Normoglycemic rats
The rats have been fasted for 12 hours. They were divided into batches of 5 rats ecah. At time T0, a blood sample was taken from the retro-orbital sinus. Physiological water (10 ml/kg, *per os*) and diethyl terephthalate (DT) (30 and 100 mg/kg, *per os*) have been administered. Blood samples have been taken every hour for 4 hours.

2.3.4.2 Glucose tolerance test
Five batches of 5 rats have been previously fasted for 12 hours. Blood samples were taken at time T-90 min, that is 90 min before glucose *per os* (4 g/kg). Immediately thereafter, the rats were fed with physiological water (10 ml/kg) and DT (30 and 100 mg/kg). At time T0, a blood sample was taken at the retro-orbital sinus followed by gavage of rats with a glucose solution at 4 g/kg. Blood samples have been taken every 30 min for 120 min.

2 .3.4.3 Type 2 diabetic rats
Type 2 diabetes was induced in normoglycemic rats by intraperitoneal (IP) injection of alloxane monohydrate solution into saline at 150 mg/kg body weight. After 72 hours, rats developed positive glucosuria, which was appreciated with Keto-Diastix test strips. A blood sample was taken to determine zero day blood glucose.

Rats with blood glucose above 2 g/L were selected and divided into 4 lots of 5:
Lot 1 (physiological serum at 10 mg/kg per os);
Lot 2 (DT: 30 mg/kg, *per os*);
Lot 3 (DT: 100 mg/kg, *per os*);
Lot 4 (glibenclamide: 0.3 mg/kg, *per os*).
The rats were fed daily, samples have been taken every other day for 8 days of observation.

2.3.5 Determination of Blood Glucose
Blood glucose levels have been determined using the *Accu-chek* glucose monitor.

2.4 Analysis and expression of results
The results have been expressed on average more or less standard error to the mean (Moy±sem). The homogeneity of the different groups was verified by variance analysis (ANOVA). The statistical comparison was done with the Student test. A value of $p<0.05$ has been set as the significance threshold, n = 5 is the number of experiments in each group.

3. RESULTS

3.1 Extraction Efficiency
The extraction efficiency of butanol-ethyl acetate fraction (BEAF) fraction is 2.32% (Table 3)

3.2 Spots and Front Reports
The various spots obtained during the CCM are recorded in Table 1.

3.3 Chemical structure of diethyl terephthalate (DT)
After analysing of the spectra of NMR experiments (1D and 2D), in comparison with data from the literature[18], the compound HD2-R1 was identified as diethyl terephthalate (DT) (Fig. 7).

3.4 Pharmacological Trials

3.4.1 Tests in Normoglycemic Rats
The administration of physiological water (10 ml/kg, *per os*) does not significantly alter the baseline blood glucose in rats (0.98±0.05 vs 0.89±0.05) (ns, n=5). Administration of DT at the dose of 30 mg/kg *per os* has no significant effect on blood glucose (0.84±0.02 vs 0.76±0.02 g/L) (ns, n=5). Under the same conditions, administration of DT at 100 mg/kg *per os* is not associated with a decrease in blood glucose (0.91±0.04 vs 0.95±0.05 g/L) (ns, n=5) (Fig. 8).

3.4.2 Glucose tolerance tests
In rats previously treated with physiological water (10 ml/kg, *per os*), the administration of glucose (4 g/kg, *per os*) induces frank hyperglycemia whose peak appears after 30 min (2.04±0.2 vs 0.81±0.06 g/L) ($p < 0.05$, n=5). Pretreatment of rats with DT (30 mg/kg, *per os*) significantly prevents a spike in hyperglycemia during a glucose tolerance test (1.24±0.2 vs 2.04±0.2 g/L) ($P<0.05$, n=5). Similarly, administration of DT at 100 mg/kg *per os* is associated with an anti-hyperglycemic effect during a glucose tolerance test (1.29±0.08 vs 2.04±0.2 g/L) ($P<0.05$, n=5) (Fig. 9).

3.4.3 Tests in Type 2 Diabetic Rats
Daily administration of DT (30 mg/kg per bone) is associated with a significant decrease in blood glucose (2±0.5 vs 3.5±0.6 g/L) after 8 days of observation. However, the prevention of hyperglycemia, in particular the variation in blood glucose decrease is more pronounced with glibenclamide, an insulin-secretory sulfonamide given at the daily dose of 0.3 mg/kg *per os* (1.63±0.19 vs 3.93±0.17) (Fig. 10).

4. DISCUSSION

Previous work had demonstrated the exclusive antihyperglycemic character of aqueous and methanol extracts of *D. guineense* leaf powder in normoglycemic rats.[15-16] Similar results were observed with the butanol-ethyl acetate fraction (BEAF) of the leaves of this plant.[17]

Diethyl terephthalate (DT), isolated from the leaves of *D. guineense*, does not alter the basic blood glucose levels of normoglycemic rats. However, it is powerfully anti-hyperglycemic in glucose tolerance test and type 2 diabetic rats to alloxane. These results suggest an exclusive anti-hyperglycemic character of DT such as some classic anti-hyperglycemic agents such as biguanides (metformin) and thiazolidinediones (rosiglitazone, pioglitazone). Therefore, it is established that DT does not stimulate the secretion of insulin such as glibenclamide but rather acts at the level of peripheral tissues like rosiglitazone and metformin, to promote glucose uptake and probably improve the action of insulin by stimulating the expression of the GLUT-4 glucose transporter.

In glucose tolerance test, DT is a powerful anti-hyperglycemic drug. Similar results were observed with metformin, an insulin-sensitizer and thiazolidinediones such as pioglitazone and rosiglitazone. Indeed, in normoglycemic mice, the prior administration of pioglitazone completely prevents the increase in blood glucose during a glucose tolerance test. This effect is also associated with increased expression in the PPAR receptor and the GLUT-4 glucose transporter. Similar temporary hyperglycemic prevention results were reported in mice pre-treated for one week with metformin, an insulinosensitizer.[19-21]

The pattern of effect on blood glucose of DT, which doesn't have effect on normoglycemic rats and prevention of temporary hyperglycemia, identical to that of metformin, rosiglitazone and pioglitazone, would involve sensitization of peripheral tissues to the action of insulin.

Alloxanic type 2 diabetes is a characteristic model of insulin secretion disorders, as opposed for example to the mouse type 2 diabetes db/db which is a model of insulin resistance whose characteristics are obesity, permanent hyperglycemia associated with hyperinsulinemia.[22] In type 2 alloxane diabetic rats, DT significantly prevents permanent hyperglycemia previously observed in the control group. However, the prevention of hyperglycemia with DT in type 2 alloxane diabetic rats is less important than that usually observed with insulin-secretors such as glibenclamide or the F5 fraction of the methanol extract from *D. guineense* leaves with hypoglycemic action.[15] Rosiglitazone, an antidiabetic agent acting on the body peripheral tissues, does not stimulate insulin secretion, induces a more pronounced prevention of hyperglycemia in insulin resistance model such as db/db mice than in type 2 diabetic rats with streptozotocin.[23] DT would help regulate blood glucose through a mechanism that involves the body peripheral tissues, which would justify, like rosiglitazone, a limited anti-hyperglycemic action of DT in insulin secretion disorder model such as alloxanic type 2 diabetes. If this hypothesis had to be confirmed, the anti-hyperglycemic action of DT would be much more marked in insulin resistance model such as db/db mouse.

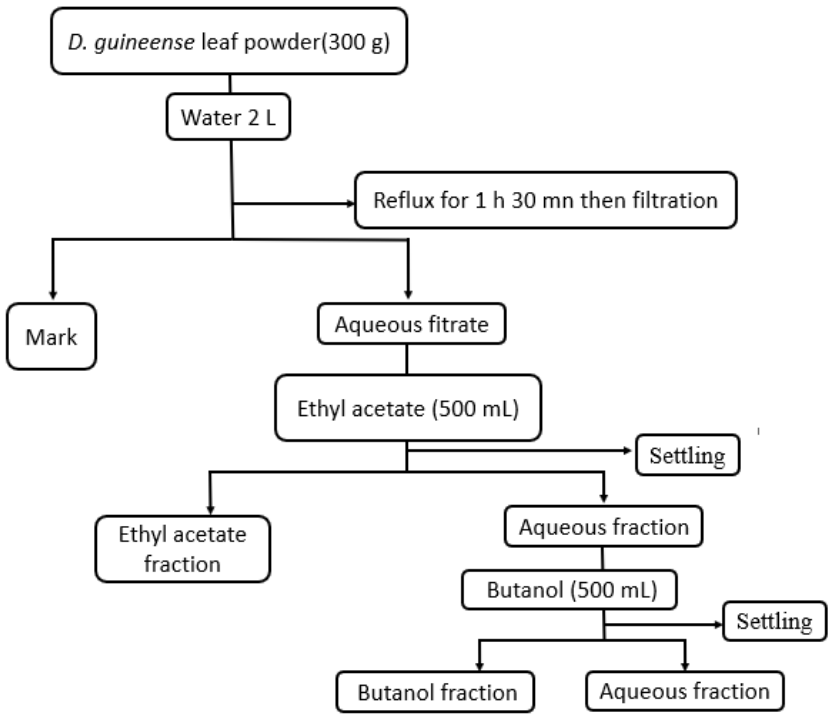

Figure 1: Extraction diagram of butanol-ethyl acetate fraction (BEAF) from *D. guineense* leaves.

Table 1: Frontal reports of isolated EABF compounds.

Spots	HD2-R1	HD2-R2	HD2-R3	HD2-R4	HD2-R5
Frontal report (Fr)	0.25	0.33	0.55	0.72	0.88
Mass (mg)	148	92	160	133	51

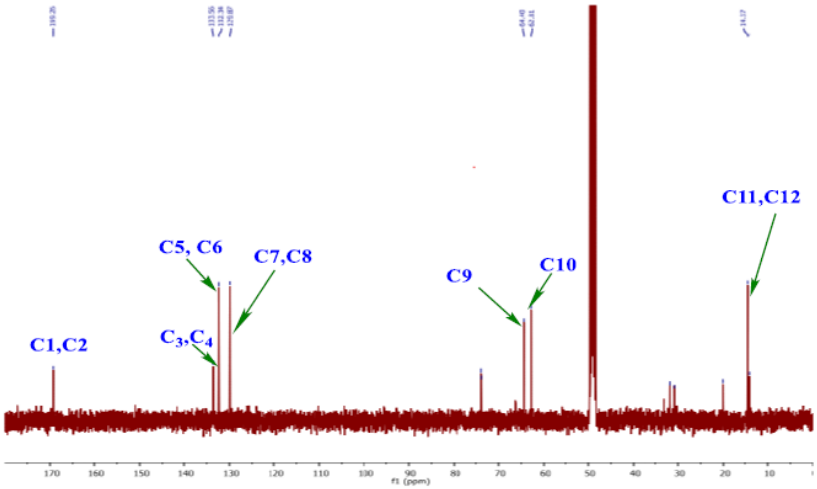

Figure 2a: Carbon spectrum of compound HD2-R1.

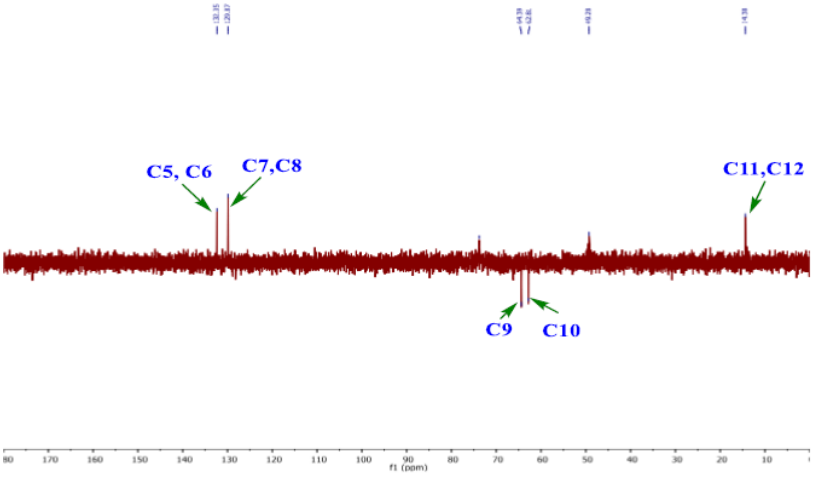

Figure 2b: DEPT 135 spectrum of HD2-R1 compound.

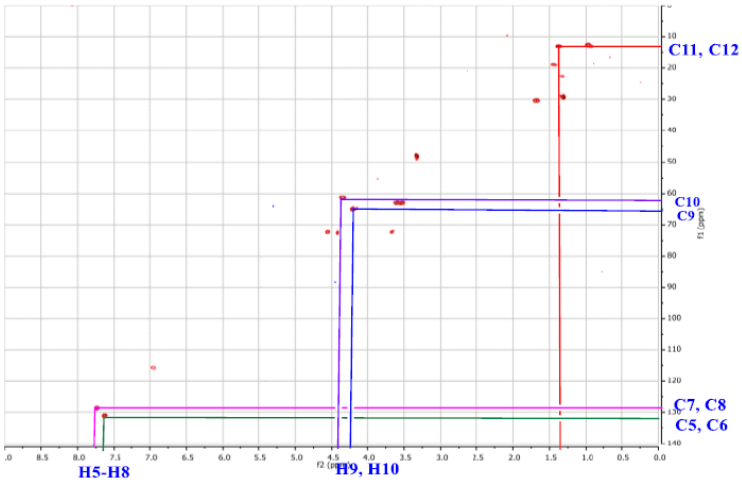

Figure 3: HSQC spectrum of HD2-R1 compound.

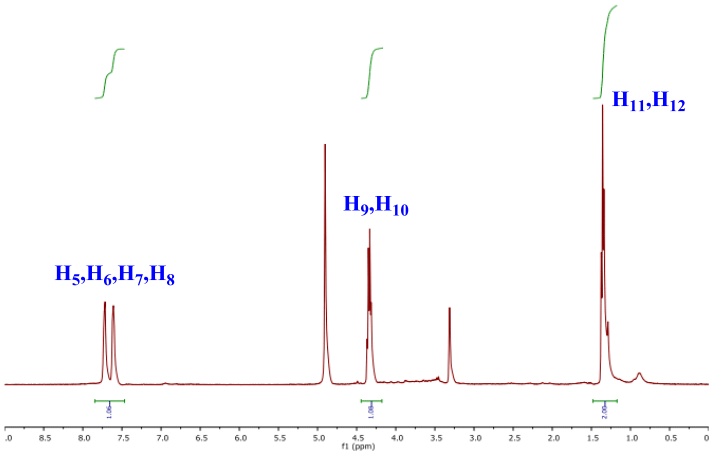

Figure 4: Proton spectrum of HD2-R1 compound.

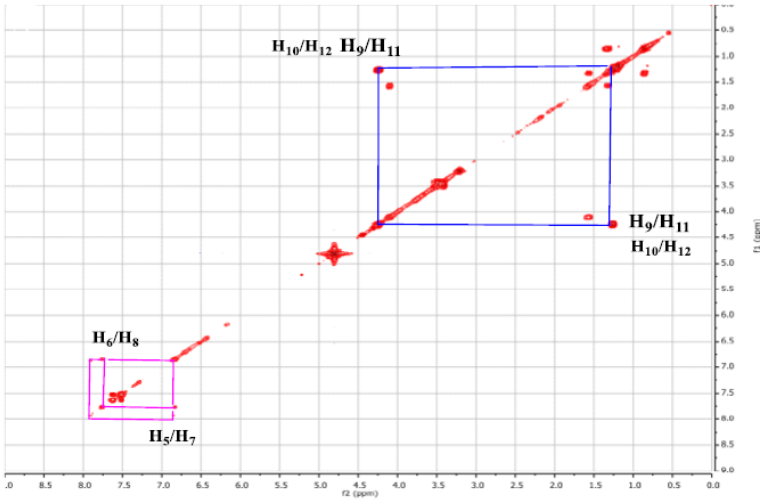

Figure 5a: HD2-R1 compound COSY spectrum.

Figure 5b: COSY fragments of the compound HD2-R1.

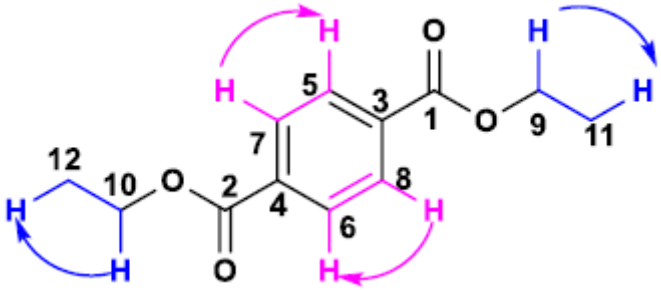

Figure 5c: HD2-R1 compound COSY correlations.

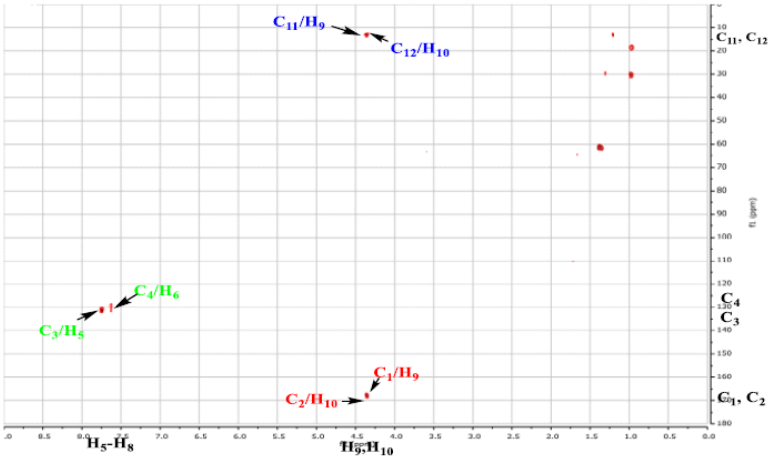

Figure 6a: HMBC spectrum of compound HD2-R1.

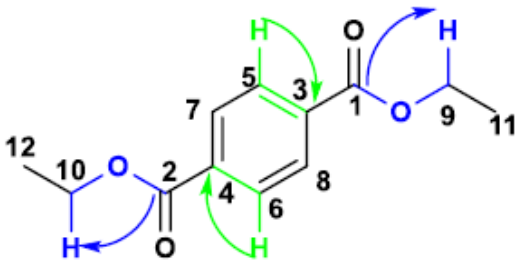

Figure 6b: HMBC correlations of HD2-R1 compound.

Table 2: Summary table of the chemical shifts of the HD2-R1 molecule.

Numéro	δ ^{13}C, ppm	δ ^{1}H, Multi. (J en Hz), ppm	Type de carbone
1	169.2		C
2	169.2		C
3	133.5		C
4	133.5		C
5	129.8	7,6 (d, 1H)	CH
6	129.8	7,6 (d,1H)	CH
7	129.8	7,6 (d, 1H)	CH
8	129.8	7,6 (d, 1H)	CH
9	62.8	4,3 (q, 2H)	CH_2
10	62.8	4,3 (q, 2H)	CH_2
11	14.3	1,3 (t, 1H)	CH_3
12	14.3	1,3 (t, 1H)	CH_3

Table 3: Extraction yield of the butanol-ethyl acetate fraction (BEAF)

Fraction	Poids(g)	Rendement (%)
Butanol-Acétate d'éthyle	6,98	2,32

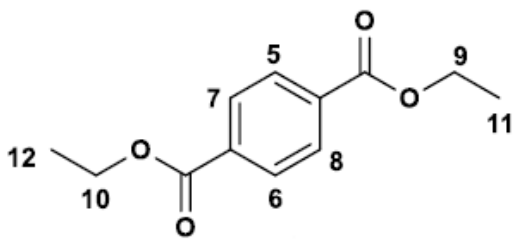

Figure 7: Structure of diethyl terephthalate (DT) ($C_{12}H_{14}O_4$)

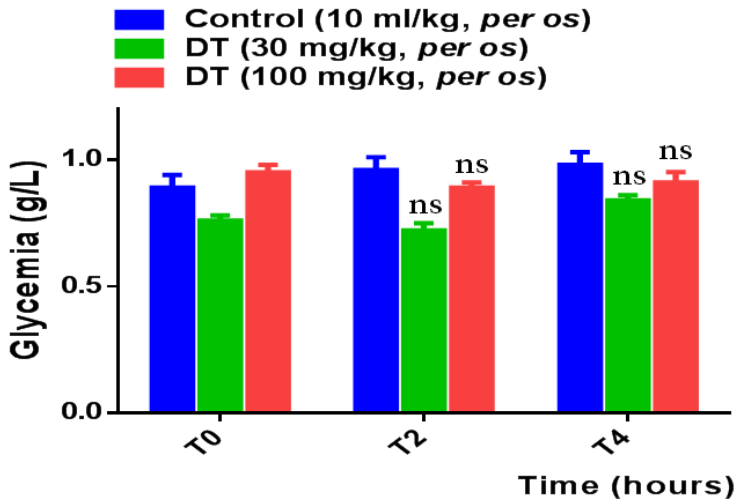

Figure 8: Changes in glycemia after administration of Diethyl terephthalate (DT) in normoglycemic rats. ns : not significant vs baseline.

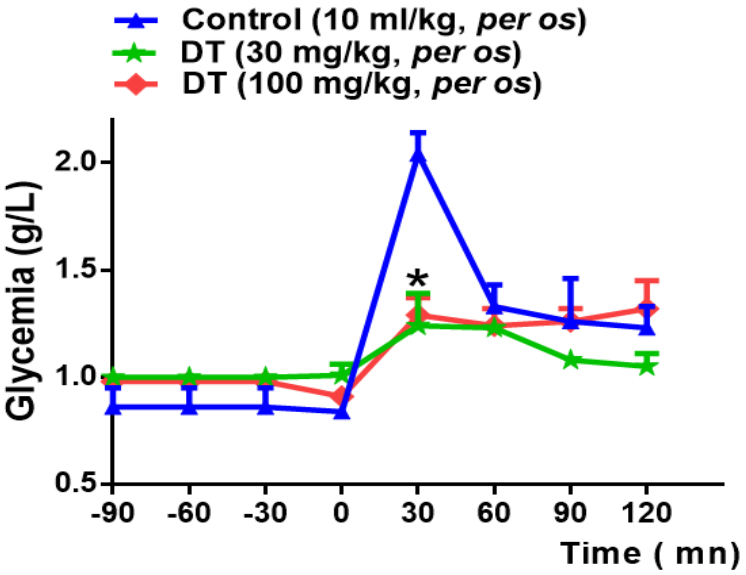

Figure 9: Anti-hyperglycemic effect of diethyl terephthalate (DT) in glucose tolerance test *p <0,05 vs contrôle.

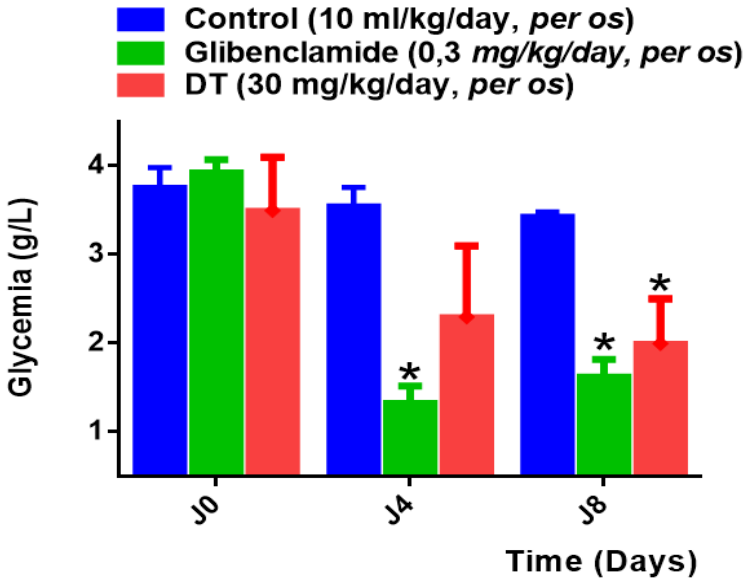

Figure 10: Anti-hyperglycemic effect of diethyl terephthalate in type 2 diabetic rats. *p <0,05 vs baseline.

5. CONCLUSION

The leaves of *D. guineense* contain diethyl terephthalate (DT), an anti-hyperglycemic molecule. The pattern of effect on blood glucose of DT is identical to that of biguanides such as metformin and thiazolidine diones, similar to rosiglitazone and pioglitazone. DT anti-hyperglycemic action would involve the body peripheral tissues.

6. REFERENCES

1. Burgering BM, Coffer PJ. Protein kinase B (c-Akt) in phosphatidylinositol-3-OH kinase signal transduction. Nature, 1995; 376: 599-2.
2. Dresner A, Laurent D, Marcucci M, Griffin ME, Dufour S, Cline GW, Shulman GI. Effects of free fatty acids on glucose transport and IRS-1-associated phosphatidylinositol 3-kinase activity. J Clin Invest, 1999; 103: 253-9.
3. Samuel VT, Shulman GI. The pathogenesis of insuline resistance: Integrating signaling pathways and substrate flux. J Clin Invest, 2016; 216: 12-2.
4. Proks P, Reimann F, Green N, Gribble F, Ashcroft F. Sulfonylurea stimulation of insulin secretion. Diabetes, 2002; 51(Suppl 3): S368-6.
5. Pathak R, Bridgeman MB. Dipeptidyl peptidase-4 (DPP-4) inhibitors in the management of diabetes. P & T, 2010; 35: 509-3.
6. Bunck MC, Cornér A, Eliasson B, Heine RJ, Shaginian RM, Taskinen MR, Smith U, Yki-Järvinen H, Diamant M. Effects of exenatide on measures of β-cell function after 3 years in metformin-treated patients with type 2 diabetes. Diabetes care, 2011; 34: 2041-7.
7. Defronzo RA, Tripathy D, Schwenke DC, Banerji M, Bray GA, Buchanan TA, et al. Prevention of diabetes with pioglitazone in ACT NOW: physiologic correlates. Diabetes, 2013; 62: 3920-6.
8. Brunton S. GLP-1 receptor agonists vs DPP-4 inhibitors for type 2 diabetes: is one approach more successful or preferable than the other? Int J Clin Pract, 2014; 68: 557-7.
9. Andreas FHP, Harald HK. The Treatment of Type 2 Diabetes. Dtsch Ärztebl Int, 2014; 111(5): 69-2.
10. Sola D, Rossi L, Schianca GPC, Maffioli P, Bigliocca M, Mella R, et al. Sulfonylureas and their use in clinical practice. Arch Med Sci, 2015; 11: 840-8.
11. Lin SH, Cheng PC, Tu ST, Hsu SR, Cheng YC, Liu YH. Effect of metformin monotherapy on serum lipid profile in statin-naïve individuals with newly diagnosed type 2 diabetes mellitus: a cohort study. Peer journal, 2018; 1-10.
12. Koumaré M. Expérience de la médecine traditionnelle dans les pays de la sous-région africaine. Première rencontre des centres collaborateurs de l'OMS de médecine Traditionnelle de la région Afrique à Niamey. Bureau régional OMS, Brazzaville, 1989.
13. Kerharo J. Pharmacopée Sénégalaise et Traditionnelle: plantes médicinales et toxiques Vigot et Frères, Paris, 1979: 1011p.
14. Olajubu F, Akpan I, Ojo D, Oluwalana S. Antimicrobial potential of *Dialium guineense* (Wild.) stem bark on some clinical isolates in Nigeria. Int J Appl Basic Med Res, 2012; 2(1): 58-2.
15. Doupa D, Ba M, Wele A, Seck SM, Barboza FS, Kane MO, Dieye PM, Diallo FA, Gueye L, Sy GY. Activité hypoglycemiante de la fraction F5 de l'extrait total méthanolique de feuilles de *Dialium guineense* (CESALPINIACEAE). Revue CAMES-SANTES, 2014; 2(1): 35-40.
16. Barboza FS, Sène M, Doupa D, Ba M, Wélé A, SY GY. Opposite effects of F1 and F5 fractions of total methanol leaf-extract of *Dialium guineense* (*Cesalpiniaceae*) on blood glucose in rat. J Adv Med Pharm Sci, 2020; 22(2): 1-8.
17. Diatta C, Diassy H, Barboza FS, Ball FS, Camara M, Gassama A, Sy GY. Effects on Blood Glucose of Ethyl Acetate-Butanol Fraction of *Dialium guineense* (Cesalpiniaceae) Aqueous Leaf Extract. J Pharm Res Int, 2022; 34(56): 77-6.
18. Hu Y, Liu J, Lü Z, Luo X, Zhang H, Lan Y, Lei A. Base-induced mechanistic variation in palladium-catalyzed carbonylation of aryl iodides. J Am Chem Soc, 2010; 132(9): 3153-8.
19. Ortsäter H, Grankvist N, Wolfram S, Kuehn N, Sjöholm A. Diet supplementation with green tea extract epigallocatechin gallate prevents progression to glucose intolerance in *db/db* mice. Nutr Metab, 2012; 9: 11-20.
20. Sato D, Morino K, Nakagawa F, Murata K, Sekine O, Beppu F, Gotoh N, Ugi S, Maegawa H. Acute Effect of Metformin on Postprandial Hypertriglyceridemia through Delayed Gastric Emptying. Int J Mol Sci, 2017; 18: 1282-2.
21. Giacoman-Martinez A, Alarcon-Aguilar FJ, Zamilpa A, Hidalgo-Figueroa S, Navarreta-Vazquez G, Garcia-Macedo R, Roman-Ramos R, Almanza-Pérez JC. Triterpenoids from Hibiscus sabariffa L. with PPARδ/γ Dual Agonist Action: *In Vivo*, *In Vitro* and *In Silico* Studies. Planta Med, 2019; 85(05): 412-3.
22. Cefalu WT. Animal Models of Type 2 Diabetes: Clinical Presentation and Pathophysiological Relevance to the Human Condition. ILAR J, 2006; 47(3): 186-8.
23. Patil KP, Kothavade P. Comparison of Rosiglitazone and Metformin in Genetically Obese and Diabetic *db/db* Mice and Streptozotocin-Iduced Diabetic Rat Models. Biomed Pharmacol J, 2018; 11(1): 325-2.