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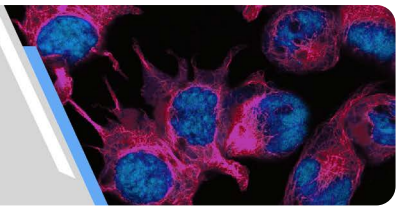

Phytochemical Profile by HPLC-MS Analysis and Antidiabetic Effects of Aqueous Extract of Trunk Bark of Lannea Microcarpa Engl. & K. Krause (Anacardiaceae) on Alloxan-Induced Diabetic Wistar Rats

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Abstract

Background and Objective: Diabetes mellitus is a chronic disease characterized by high blood glucose due to poor insulin secretion or pancreatic beta cells' absorption and constitutes a public health problem. Multiple approaches have been adopted to combat this pathology, including the search for new bioactive compounds. This study aimed to evaluate *in vivo*, the antihyperglycemic effects of the Lm extract of *Lannea microcarpa* trunk bark on an alloxan-induced diabetic Wistar rat model.

Methods: To achieve the results, a phytochemical screening of secondary metabolites in the extract was performed using the HPLC-MS method. The hyperglycemic state was induced in rats by a single administration of Allox intraperitoneally, and the effects of Lm5, Lm25, and Glib were investigated.

Results: Phytochemical analysis revealed the presence of flavonols, isoflavonoids, and hydrocinnamic acid derivatives. Pharmacologically, the extract significantly reduced blood glucose. After 4 days oral administration of Lm5 and Lm25, blood glucose in diabetic rats was significantly reduced more than 70%, from 228.67±25.82 mg/dL to 112.33±33.152 mg/dL for the Allox+Lm5 and from 261.83±24.17 mg/dL to 99.33±14.72 mg/dL for the Allox+Lm25 groups versus the Allox alone group (240±30.95 mg/dL to 268.4±30.57 mg/dL, $p<0.001$). The Glib5 reduced hyperglycemia in diabetic rats by 57%, from 254.67±31.08 mg/dL to 121.5±35.69 mg/dL, compared with the Allox alone group (240±30.95 mg/dL to 268.4±30.57 mg/dL) over the same study period ($p<0.001$). In addition, at baseline, all rats' groups had homogeneous blood glucose levels (80.67±3.00 mg/dL, 81.33±8.59 mg/dL, and 77.83±4.70 mg/dL for the NaCl 0.9% control, Lm5 and Lm25 groups, respectively). Blood glucose levels in these rats' groups did not vary significantly throughout the experiment. Interestingly, this extract normalized food and water consumption and attenuated organ hypertrophy in diabetic rats.

Conclusion: The Lm extract of *L. microcarpa* trunk bark has antidiabetic therapeutic potential attributable to its bioactive compounds contained.

Keywords: *Lannea macrocarpa*, HPLC-MS, Diabetes, Antihyperglycemic, Hypoglycemic, Wistar rat.

Introduction

Diabetes mellitus, a chronic disease characterized by high blood sugar

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levels due to low insulin secretion or low insulin uptake by cells due to resistance mechanisms, is a global health concern. The global prevalence of diabetes is alarming and continues to rise [1]. Indeed, the global prevalence of diabetes in the 20-79 age group in 2021 was estimated at 10.5% (536.6 million people), rising to 12.2% (783.2 million) in 2045 [2]. In sub-Saharan Africa, there were an estimated 15.5 million diabetics in 2017, with nearly 300,000 deaths "IFD, 2017" and a projected 41.4 million in 2025, an increase of 109% [3]. In Burkina Faso, its prevalence has been estimated at 4.9% in the general population [4], 13.9% in urban areas [5], and 5.7% in rural areas [6]. According to a study by the Global Burden of Diseases, type 2 diabetes, in correlation with its complications, is responsible for a significant increase in cases of disability (22%) over the last 10 years [2, 7]. Studies have shown that diabetic patients frequently develop complications such as retinopathy, nephropathy, atherosclerosis, vascular disorders, blindness, and renal failure [8, 9].

Severe complications can lead to death, especially in the context of COVID-19. Treatment is lifelong and requires constant monitoring. Moreover, modern, expensive drugs are difficult to access. Indeed, global healthcare expenditure on diabetes has been estimated at $966 billion in 2021 and is expected to reach $1,054 billion by 2045 [2]. Thus, to combat this epidemic, a multi-faceted approach, including prevention, early diagnosis, effective management, and research into new bioactive compounds, is essential [10]. This has renewed worldwide attention and interest in traditional medicine, whose plants constitute a rich reservoir of bioactive compounds [11]. These natural compounds offer promising avenues for the development of new anti-diabetic therapies. With this in mind, the "Institut de recherche en Sciences de la Santé (IRSS)" in Burkina Faso has a database of medicinal recipes used in the management of metabolic diseases, including diabetes [12, 13]. However, the lack of preclinical anti-diabetic scientific data makes it impossible to judge the efficacy of these medicinal recipes. One such recipe is *Lannea microcarpa* Engl. and K. Krause (Anacardiaceae), a species belonging to the Anacardiaceae family, has attracted much attention. Studies have shown that the Lannea genus, *Lannea edulis*, possesses anti-diabetic properties through the inhibition of alpha-amylase [14].

In addition, work carried out on *Lannea microcarpa* (*L. microcarpa*) extracts have highlighted certain phytochemical groups and molecules. The presence of triterpene sterols, anthracenosides, steroidal and triterpene glycosides, coumarin derivatives, saponosides, reducing compounds, anthocyanins, and phenolic compounds (tannins) have been highlighted in *L. microcarpa* trunk bark [15, 16]. The plant's fruits contain total polyphenols as well as flavonoids. In addition, 4'-methoxy-myricetin 3-O-α-L-rhamnopyranoside, vitexin, isovitexin, myricetin 3-O-α-L-rhamnopyranoside, myricetin 3-O-α-L- glucopyranoside, gallic acid, and epi-catechin have been identified in *L. microcarpa* leaves. Three (03) major molecules in the n-butanol fraction of *L. microcarpa* leaves have been isolated [17, 18]. Cyanidin 3-0-(2-0-β-D-xylopyranosyl) β-D-galactopyranoside, cyanidin 3-0-β-D-galactopyranoside, and anthocyanin have also been identified in the epicarp of dried fruits. Seed oils have also highlighted compounds such as γ-tocopherol, α-tocopherol, and δ-tocopherol [18]. Extracts (freeze-dried aqueous and its fractions) of *L. microcarpa* trunk bark [16, 19], leaves, and fruit [20, 21] possess antioxidant properties. In addition, *L. microcarpa* leaf and trunk bark extracts have anti-inflammatory properties [17, 22].

The aqueous extract (LMaq) and its dichloromethane and ethyl acetate fractions of *L. microcarpa* trunk bark possess concentration-dependent and endothelium-independent vasorelaxant properties in Wistar rats. This vasorelaxant property is partly due to the inhibition of phosphodiesterase [15] and intracellular calcium release [16]. Also, the ethyl acetate moiety prevents angiotensin II-induced hypertension. The effects were associated with reduced COX-2 and NOX-2 expression of NADPH oxidase in aortas by western blot [16]. Bark extracts have moderate diuretic activity [23] and antihypertensive effects [24]. These works show that the plant possesses biological effects counteracting metabolic pathologies. However, no scientific findings on these anti-diabetic properties have yet been found. This research, therefore, aims to contribute to the development of natural approaches to diabetes management by evaluating the antihyperglycemic properties of the aqueous extract derived from *L. macrocarpa* trunk bark in a rat model of diabetes induced by alloxan, a toxic substance that destroys pancreatic beta cells.

Material and Methods

Material

Chemicals

Alloxan monohydrate and NaCl were obtained from Sigma Aldrich Company (Merck KGaA, Darmstadt, Germany). Total cholesterol, HDL-cholesterol, LDL-cholesterol, and Triglycerides were from SPINREACT (Sant Esteve de Bas, Gerona, Spain). Neu's reagent, $FeCl_3$, Sulfuric anisaldehyde, and Liebermann Bürchard's reagent were from Sigma Alrich (France).

Collection of plant material

The bark of the trunk of *Lannea microcarpa* was collected in the locality of Loumbila, located 20 km northeast of the center of Ouagadougou, Burkina Faso. After harvest, the samples were rinsed, dried away from sunlight, and made into

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powder using a mechanical grinder. A sample was collected and deposited at the herbarium of the National Centre for Scientific and Technological Research under the number HNBU 361.

Animals

Adult male rats of Wistar strains, 12 weeks old and weighing 247.33±9.79 g, were used in this study. These animals were obtained from CIRDES and then acclimated at the IRSS animal facility for one week in polycarbonate cages with wood shavings as bedding before use. They were fed wheat meal (29%) with free access to running water under standard conditions of temperature (23±2°C) with relative humidity (60-70%) followed by a 12 h light/dark cycle. All experiments were carried out following the procedures of the Guide to Good Practice in Animal Experimentation under the Declaration of Helsinki [129], which is in line with the terms of the Local Ethics Committee of Joseph KI-ZERBO University (Protocol number: CE-UJKZ/2024-05).

Methods

Aqueous decoction preparation

100 g of plant bark powder was diluted in 500 mL of distilled water, boiled for 30 minutes, and then cooled to room temperature. After cooling, the mixture obtained was centrifuged at 3000 rpm for 5 minutes. The aqueous decoction supernatant was collected, frozen, and freeze-dried. The lyophilized aqueous decoction of *Lannea microcarpa* trunk bark (Lm) was then used for the experiments.

Phytochemical screening HPLC-MS

Phytochemical screening of metabolites was carried out using high-performance liquid chromatography (HPLC) coupled with mass spectrometry. Specifically, an HPLC chain (Agilent 1290, San Jose, USA) equipped with a G7104A pump was combined with a G7167B autosampler. The HPLC chain was coupled with a mass spectrometer (Agilent 6545, San Jose, USA). The ionization source was a continuous jet (Electrospray ionization) in negative mode (ESI-). Phenolic compounds were detected over a pressure limit (0-1300 bar). For spectra recording, 2 µL of Lm extract solution was injected into a C18 column of size 2.1× 50 mm and internal diameter 1.8 µm (brand Zorbax RRHD Eclipse Plus C18, Agilent, USA) for compound separation. The mobile phase comprised two solvents (solvent A + solvent B). Solvent A consisted of acidified water and 0.1% formic acid. Solvent B was acrylonitrile (100%). The gradient profile was: 0-7 min (70% A + 30% B); 7-8 min (40% A + 60% B); 8-10 min (38% A + 62% B); 10-15min (30%A + 70% B) and after 15 min (70% A + 30% B). The mobile phase flow rate was set in continuous mode at 0.1 ml/min for the duration of the analysis.

Pharmacology study

Induction of diabetes in experimental rats

Type 2 diabetes was induced according to the methods described by Banda et al., 2018 with slight modifications [14]. Briefly, male Wistar rats were fasted on a water diet for 12 hours, and then fasting blood sugar was determined to range from 60 – 120 mg/dL, which was considered normal. A solution of monohydrate alloxan in NaCl 0.9% was prepared extemporaneously and then administered to the animals intraperitoneally (dose of 150 mg/kg body weight). A comparable volume of 0.9% NaCl was administered to control animals. A glucose solution (10%) was added to the water to prevent hypoglycemia attacks. Seventy-two hours (72 h) after the alloxan injection, all animals' fasting blood sugar levels were determined, and only those with blood sugar levels greater than or equal to 200 mg/dL were considered diabetic.

Administration of tests substances

After the induction of diabetes, 7 groups of six homogeneous rats each, including 04 from diabetic rats and 3 from normal rats, were formed. The administration of the substances was carried out according to the following design:

Group 1 = Control: Administration of NaCl 0.9% alone for 04 weeks;

Group 2 = Allox: Single administration of Alloxan 150 mg/kg bw and followed for 04 weeks;

Group 3 = Lm5: Administration of Lm 5 mg/kg/day alone for 04 weeks;

Group 4 = Lm25: Administration of Lm 25 mg/kg/day alone for 04 weeks;

Group 5 = Allox+Glib: Single administration of Alloxan 150 mg/kg bw + Administration of glibenclamide 5 mg/kg/day for 04 weeks;

Group 6 = Allox+Lm5: Single administration of Alloxan 150 mg/kg bw + Administration of Lm 5 mg/kg/day alone for 04 weeks;

Group 7 = Allox+Lm25: Single administration of Alloxan 150 mg/kg bw + Administration of Lm 25 mg/kg/day alone for 04 weeks.

At the end of the experimental period and 24 hours after the last treatment, the different animals were anesthetized, and blood was collected by cardiac puncture. They were then humanely sacrificed, and the heart, liver, kidneys, spleen, and testicles were removed and weighed. Serum was collected for biochemical analyses. The organs were preserved for subsequent histopathological analyses.

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Blood glucose determination

Following the first measurement, the blood sugar of each animal was determined every 04 days by the caudal puncture method for 28 days using an Accu-Chek glucometer (brand). After each sample, the animal's tail was disinfected using alcohol.

Boody weight, Water, and Feed intake measurement

The effects of Lm5, Lm25, Allox, Allox+Lm5, Allox+Lm25, Allox+Glib, and physiological water (NaCl 0.9%) on the evolution of body weight, water, and feed intake during the study were determined. For that, the body weights of all animals were recorded at inclusion and were divided into 7 homogeneous batches of six (06) animals, including a control batch. During the experiment, the average weight of each batch was recorded with a periodicity of 4 days until the 28th day using an electronic scale. Water and feed consumption per lot of animals was measured at inclusion, followed by a periodic interval of four (04) days throughout the experiment period.

Liver lipid profile analysis

At the end of the experiment, the animals were humanely sacrificed. Blood was drawn, and serum was collected after centrifugation at 4,000 rpm for 05 min and stored at 4°C. These samples were then used for the determination of total cholesterol (TC), low-density lipoprotein (LDL), triglycerides (TG) and high-density lipoprotein (HDL) levels.

Statistical analysis

All data collected during the experiment were subjected to statistical analysis using GraphPad Prism 8.01 software. Results were expressed as mean ± SEM between the experimental and normal control groups after one- and two-way analysis of variance (ANOVA) followed by the Bonferroni post-test. A statistically significant difference was considered when the p-value < 0.05.

Results

Phytochemical screening of Lm extract from *L. microcarpa* trunk bark

The chromatogram of the Lm extract obtained by HPLC-MS shows five major peaks with retention times of 0.571, 7.787, 9.028, 10.580, and 13.606, respectively (figure 1).

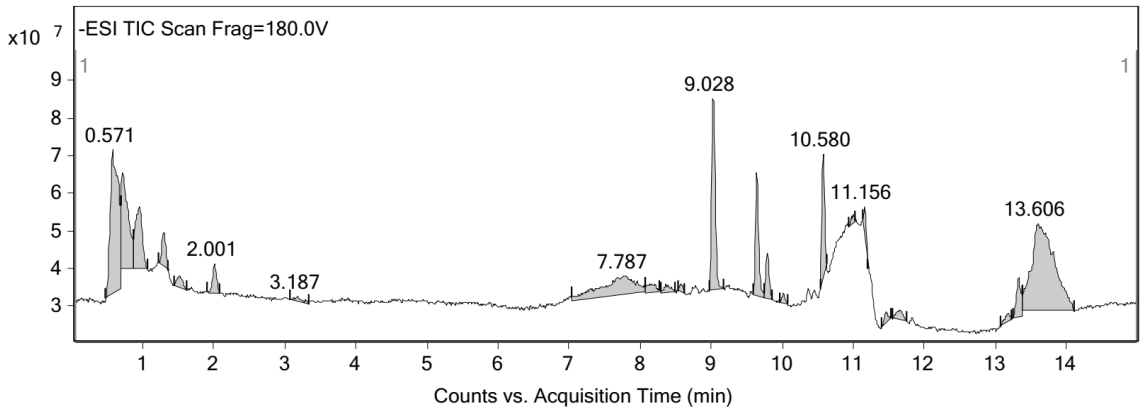

Figure 1: Chromatogram HPLC-MS of Lm extract of *Lannea microcarpa* trunk bark

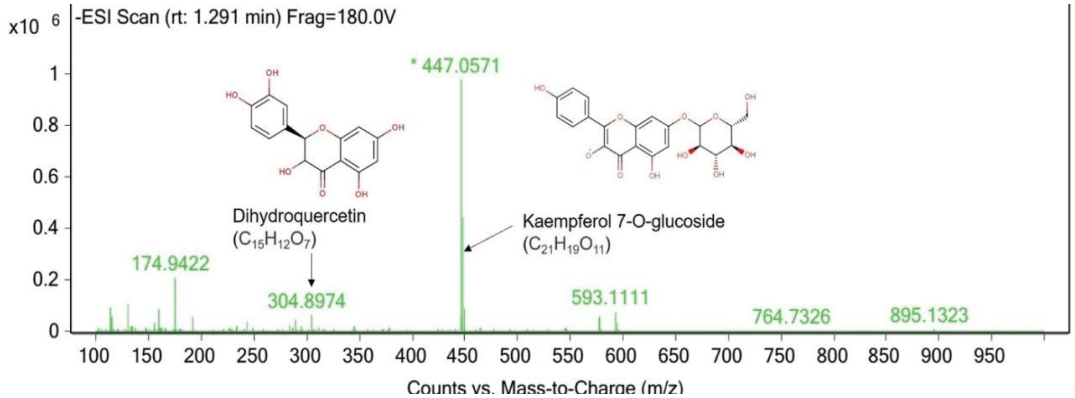

Figure 2: Mass spectrum of Lm extract of *Lannea microcarpa* trunk bark at RT 1.291 min

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Phenolic compound identification in Lm extract of *L. microcarpa* trunk bark

Analysis of the mass spectra of the various peaks present on the chromatogram showed numerous fragments of varying height and density. Mass identification (m/z) revealed the presence of natural compounds of interest, including flavanols, isoflavonoids, and hydrocinnamic acid derivatives. Comparison of the m/z = 304.8974 and m/z = 447.0571 fragments of the peak observed at retention time 1.291 min and m/z = 353.1916 with data from ChemSpider, Pubchem, Dictionary of Natural Products, and Phenol Explorer enabled a match to be found. This preliminary process enabled us to identify dihydroquercetin (theoretical m/z = 304.051), kaempferol 7-O-glucoside (theoretical m/z = 447.0927) and 3 caffeoylquinic acid or neochlorogenic acid (theoretical m/z = 354.0950) in close agreement with the experimental m/z masses of 304.8974, 447.0571 and 353.1916 respectively. This identification remains provisional pending consideration of the fragmentation mechanics and explanation of the possible losses [M-H], [M-H2O], and [M-Na] involved in the constitution of each molecule. Figure 2 shows the mass spectrum of the peak observed at a retention time of 1.291 min and the molecular formulas of dihydroquercetin and kaempferol 7-O-glucoside identified through the databases.

Figure 3 shows the mass spectrum of the peak observed at a retention time of 9.782 min and the caffeoylquinic acid or neochlorogenic compound identified through the databases.

Other natural phenolic compound identification

More than ten compounds of interest were tentatively identified following the same identification process by comparing the experimental and theoretical m/z masses of fragments obtained by HPLC-MS of the Lm extract of *L. microcarpa*. However, the identification process for these compounds did not include the mass loss process. Table I summarizes the retention times, masses, and formulae of compounds provisionally identified by MS fragmentation of the Lm extract.

Pharmacological evaluation of the anti-diabetic effects of Lm extract of *L. microcarpa*

Anti-hyperglycemic effect of Lm extract of *L. microcarpa* on diabetic-induced Wistar rat

The effects of Lm5 and Lm25 extracts and Glib on alloxan-induced hyperglycemia are shown in Figure 4. All groups of rats had homogeneous blood sugar levels at baseline (80.67±3.00 mg/dL, 76.20±3.76 mg/dL, 84.83±6.83 mg/dL, 79±5.33 mg/dL and 77.83±3.06 mg/dL for the control groups, Alloxan alone, Allox+Glib, Allox+Lm5 and Allox+Lm25 respectively). After eight days of Alloxan administration, blood sugar levels in the different animals increased significantly with blood sugar values of 240±30.95 mg/dL, 254.67±31.08 mg/dL, 228.67±25.82 mg/dL and 261.83±24.17 mg/dL respectively for the Allox, Allox+Glib, Allox+Lm5 and Allox+Lm25 groups compared with those of the control group NaCl (78.33±6.11 mg/dL). After 4 days of oral administration of Lm5 and Lm25, blood glucose levels in diabetic rats were significantly decreased by more than 70%, 228.67±25.82 mg/dL to 112.33±33.152 mg/dL for the Allox+Lm5 group and 261.83±24.17 mg/dL to 99.33±14.72 mg/dL for the Allox+Lm25 group compared with the Allox alone group 268.4±30.57 mg/dL ($p<0.001$). In addition, glibenclamide (5 mg/kg/day) taken as a positive reference reduced hyperglycemia in the rats by 57% from 254.67±31.08 mg/dL to 121.5±35.69 mg/dL compared with the Allox alone group (240±30.95 mg/dL to 268.4±30.57 mg/dL) over the same period ($p<0.001$).

Hypoglycemic effect Lm extract of *Lannea microcarpa* on normal rat blood sugar level

Figure 5 shows the effect of the Lm extract of *L. microcarpa* (5 mg/kg and 25 mg/kg) and NaCl 0.9% on blood sugar levels in normal rats and diabetic rats induced by alloxan. At inclusion, all groups of rats had homogeneous blood sugar levels at baseline (80.67±3.00 mg/dL, 81.33± 8.59 mg/dL, 77.83±4.70 mg/dL, and 76.20±3.76 mg/dL for the control NaCl 0,9%, group, Lm5 group, Lm25 group

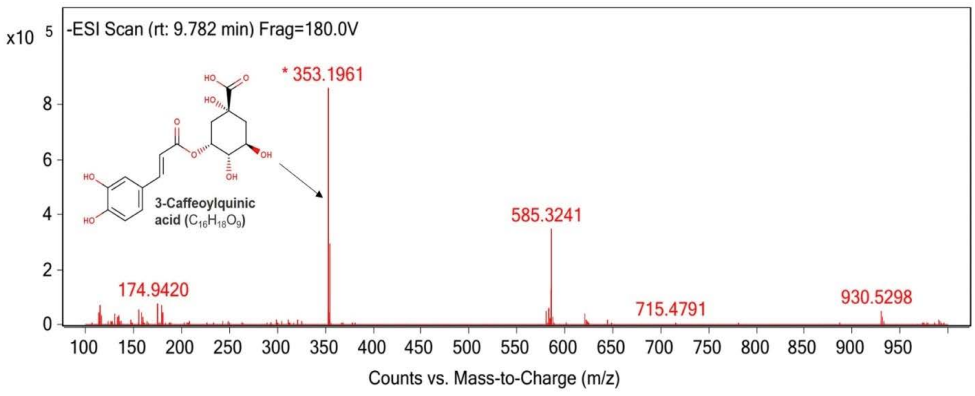

Figure 3: Mass spectrum of Lm extract of *Lannea microcarpa* trunk bark at RT 9.782 min

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Table I: Natural compounds provisionally identified in Lm extract of *Lannea microcarpa*

RT (min)	m/z exp	m/z theo	Proposed compounds	Formula
0.571	405.0837	404.11	Resveratrol-3-O-glucuronide	$C_{20}H_{20}O_9$
0.571	259.0151	258.08	3,4,7-Trihydroxyisoflavone	$C_{15}H_{14}O_4$
0.571	533.1532	534.1	kaempferol 3-O-(6-malonylglucoside)	$C_{24}H_{22}O_{14}$
0.715	289.0552	288.0633	3,4,5,7-Tetrahydroxyisoflavone	$C_{15}H_{12}O_6$
2.001	304.897	340.051	Dihydroquercetin	$C_{15}H_{12}O_7$
2.001	696.7541	697.1616	Cyanidin 3-O-(6''-malonyl-3''-glucosyl-glucoside)	$C_{30}H_{33}O_{19}$
9.028	174.9422	174.0316	juglone	$C_{10}H_6O_3$
9.028	316.9189	316.0583	Isorhamnetin	$C_{16}H_{12}O_7$
9.028	520.3664	521.4475	Petunidin 3-O-(6''-acetyl-galactoside)	$C_{24}H_{25}O_{13}$
9.028	758.0357	757.2191	Cyanidin 3-O-glucosyl-rutinoside	$C_{33}H_{41}O_{20}$
10.58	163.0993	164.04734	p-Coumaric acid	$C_9H_8O_3$
10.58	339.2275	340.3698	8-Prenylnaringenin	$C_{20}H_{20}O_5$
10.58	653.3852	654.527	Hesperetin 3',7-O-diglucuronide	$C_{28}H_{30}O_{18}$
10.58	757.4234	757.2191	Cyanidin 3-O-glucosyl-rutinoside	$C_{33}H_{41}O_{20}$

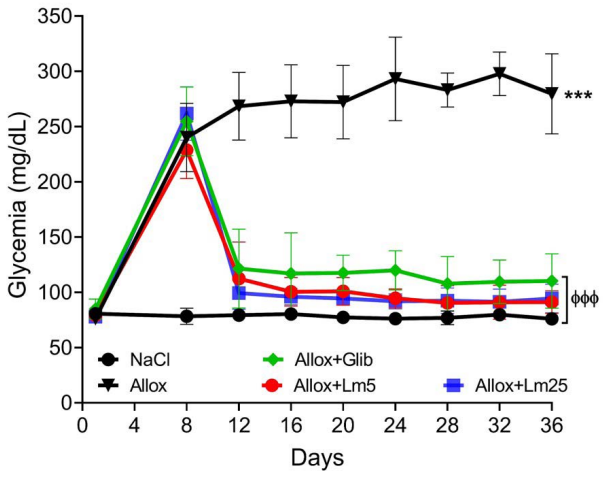

Figure 4: Antihyperglycemic effects of Lm extract of *Lannea microcarpa* and glibenclamide after 4 weeks of treatment of diabetic rats with alloxan. Results are expressed as mean ± SEM (n = 6/group); ***p < 0.001 vs Control NaCl 0.9% group and ϕϕϕp<0.001 vs Alloxan group. With: *NaCl : NaCl 0.9% ; Lm5 : Lm 5 mg/kg/day ; Lm25 : Lm 25 mg/kg/day; Allox: Alloxan 150 mg/kg; Allox+Glib: Alloxan 150 mg/kg+ Glibenclamide 5 mg/kg/day ; Allox+Lm5 : Alloxan 150 mg/kg+Lm 5 mg/kg/day; Allox+Lm25 : Alloxan 150 mg/kg+Lm 25 mg/kg/day*

and Alloxan alone respectively. The blood glucose levels of the different groups of rats did not change significantly throughout the experiment, except for the Alloxan group. The blood glucose level in the alloxan group (240±30.95 mg/dL) increased significantly after 04 days of alloxan administration at a dose of 150 mg/kg. This increase was maintained until the 28th day of the experiment (268.4±30.57 mg/dL).

Effect of Lm extract of *Lannea microcarpa* on the average rat's body weight gain

Figure 6 shows the effects on body weight of Lm extract of *L. microcarpa*, alloxan, and glibenclamide on diabetic and non-diabetic rats during the experimental period. At the

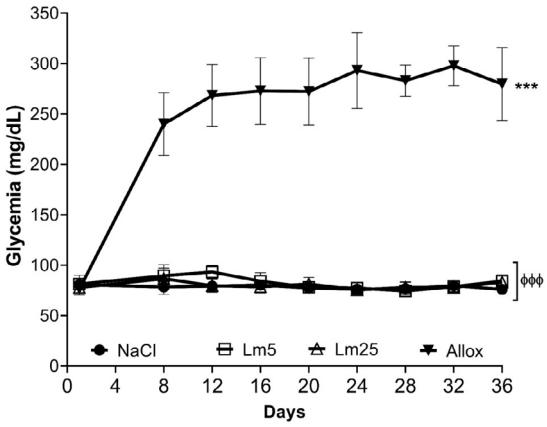

Figure 5: Hypoglycemic effects of control NaCl 0.9% group, Lm extract of *Lannea microcarpa* groups, and Alloxan group after 04 weeks treatment on normal Wistar rat. Results are expressed as mean ± SEM (n = 6/group); ***p < 0.001 versus Control NaCl 0.9% group and ϕϕϕp<0.001 vs Alloxan group. *With: NaCl:* NaCl 0.9% ; *Lm5: Lm 5 mg/kg/day ; Lm25: Lm 25 mg/kg/day; Allox: Alloxan 150 mg/kg*

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start of the study, all groups of rats showed a homogeneous mass. Figure 6A shows that the extracts at daily doses of 5 and 25 mg/kg bw did not significantly change the weight of the animals compared with that of the 0.9% NaCl control group. Indeed, after 28 days of inclusion, the weight gain of the rats was 33.67±10.57%, 27.33±4.88%, and 25.83±5.38%, respectively, for the Lm5, Lm25, and NaCl 0.9% control groups ($p<0.001$). However, induction of diabetes by Alloxan administration resulted in a significant weight loss in rats compared to the NaCl control group ($p<0.001$) (figure 6B). On day 20 of the experiment, the weight of the rats was -54.4±8.90%, -34.83±4.62%, -43.33±6.65%, and -44.17±7.83%, respectively, for the Allox, Allox+Glib, Allox+Lm5, and Allox+Lm25 groups compared with the 0.9% NaCl group (+18.83±10.72%). Finally, treatment of diabetic rats for 04 weeks with Lm5, Lm25, and Glib significantly increased the weight of rats that were losing weight. Indeed, at the end of the experiment, a slight but significant weight gain was then progressively observed for the Allox+Glib (-29.5±7.36%), Allox+Lm5 (-39±7.84%), and Allox+Lm25 (-35.83±6.43%) groups compared with the Allox group (-77.4±6.19%).

Effect of Lm extract of *Lannea microcarpa* on animal's average water consumption

Table II shows the water intake of study rats during daily administration of NaCl 0.9%, Lm5, and Lm25 extracts, Glib, and Allox. Water consumption in healthy rats was between animals in the control (94.79±1.56 mL/rat), Lm5 (90.62±1.56 mL/rat), and Lm25(91.67±05 mL/rat) groups during the experiment ($p>0.05$). However, the water consumption of the alloxan-induced diabetic rats was significantly greater than that of the control group (94.79±1.56 mL/rat) ($p<0.001$). The treatment resulted in a significant ($p<0.001$) decrease in water consumption in the Allox+Lm5 (113.54±1.56 mL/Rat) and Allox+Lm25 (110.42±2.08 mL/Rat) and Allox+Glib (114.58±2.08 mL/Rat) groups compared with the Allox group (220.83±00 mL/Rat). Table III also shows the food intake of the experimental rats. Food intake was significantly higher in the Allox diabetic control rats (32.81±0.85 g/Rat) than in the non-diabetic NaCl rats (94.79±1.56 g/Rat) ($p<0.001$). Interestingly, supplementation with Lm5 (113.54±1.56 g/Rat) and Lm25 (110.42±2.08 g/Rat) reduced the increase in food intake observed in treated diabetic animals compared with control diabetic rats from day 16 onwards. This effect was similar in the Allox+Glib group (114.58±2.08 g/Rat).

Effect of the Lm extract of *Lannea microcarpa* on average organ weight

Vital organs such as the heart, lungs, liver, spleen, kidneys, and testes of the rats in the experiment were weighed (Figure 7). The Lm extract had no particular impact on the noble organs of the healthy rats in the study. However, induction of diabetes with Alloxan resulted in hypertrophy of the noble organs compared with non-diabetic rats ($p<0.001$). However, it should be noted that Lm5, Lm25, and Glib reduced the hypertrophy observed in the diabetic control group. The relative organ weights of treated diabetic rats were similar to those of the NaCl control group ($p>0.05$).

Effect of the Lm extract of *Lannea microcarpa* on treated rats' liver

Table IV shows the effect of lyophilized aqueous extract of *L. microcarpa*, alloxan, and glibenclamide on plasma lipid levels in rats during the experiment. In addition, the various substances did not produce any particular changes in plasma lipid levels. Thus, over a 4-week period, total cholesterol, HDL, triglyceride, and LDL levels did not vary significantly from the NaCl control, irrespective of the physiological state of the rats.

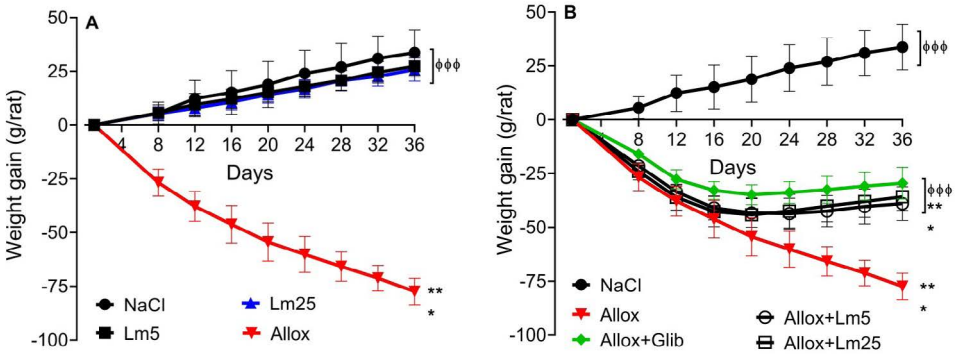

Figure 6: Effects of Lm extract of *Lannea microcarpa*, NaCl 0.9%, Alloxan, and glibenclamide on weight changes in normal rats during experimentation. Results are expressed as mean ± SEM (n = 6/group); ***$p < 0.001$ versus Control NaCl 0.9% group and $^{ϕϕϕ}p<0.001$ vs Alloxan group. With: *NaCl : NaCl 0.9% ; Lm5 : Lm 5 mg/kg/day ; Lm25 : Lm 25 mg/kg/day; Allox: Alloxan 150 mg/kg; Allox+Glib: Alloxan 150 mg/kg+ Glibenclamide 5 mg/kg/day ; Allox+Lm5 : Alloxan 150 mg/kg+Lm 5 mg/kg/day; Allox+Lm25 : Alloxan 150 mg/kg+Lm 25 mg/kg/day*

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Table II: Effect of 0.9% NaCl, Lm extract of *Lannea microcarpa*, glibenclamide, and Alloxan on mean water consumption of animals during the experiment (n = 6).

Average water consumption during the various treatments (mL/Rat)							
Average days	**NaCl**	**Lm5**	**Lm25**	**Allox**	**Allox+Glib**	**Allox+Lm5**	**Allox+Lm25**
8	64.29±2.04$^{\phi\phi\phi}$	60.12±2.04$^{\phi\phi\phi}$	64.88±2.04$^{\phi\phi\phi}$	170.24±36.39***	164.29±40.81***	173.81±37.41***	178.57±43.7***
12	68.75±2.08$^{\phi\phi\phi}$	63.54±1.56$^{\phi\phi\phi}$	68.75±2.08$^{\phi\phi\phi}$	204.17±4.17***	187.5±12.5***	204.17±6.25***	193.75±7.29***
16	70.83±00 $^{\phi\phi\phi}$	66.67±00$^{\phi\phi\phi}$	70.83±00$^{\phi\phi\phi}$	208.33±00***	170.83±2.08$^{***\phi\phi\phi}$	177.08±6.25$^{***\phi\phi\phi}$	177.08±6.25$^{***\phi\phi\phi}$
20	75±00$^{\phi\phi\phi}$	69.79±1.56$^{\phi\phi\phi}$	72.92±2.08$^{\phi\phi\phi}$	212.5±4.17***	150±12.5$^{***\phi\phi\phi}$	162.5±4.17$^{***\phi\phi\phi}$	154.17±6.25$^{***\phi\phi\phi}$
24	79.17±2.08$^{\phi\phi\phi}$	73.96±1.56$^{\phi\phi\phi}$	79.17±2.08$^{\phi\phi\phi}$	219.79±1.56***	130.21±1.56$^{***\phi\phi\phi}$	142.71±3.65$^{***\phi\phi\phi}$	141.67±00$^{***\phi\phi\phi}$
28	87.5±00$^{\phi\phi\phi}$	80.21±1.56$^{\phi\phi\phi}$	84.37±1.56$^{\phi\phi\phi}$	220.83±00***	128.13±1.56$^{***\phi\phi\phi}$	127.08±2.08$^{***\phi\phi\phi}$	129.17±4.17$^{***\phi\phi\phi}$
32	90.62±1.56$^{\phi\phi\phi}$	85.42±2.08$^{\phi\phi\phi}$	88.54±1.56$^{\phi\phi\phi}$	220.83±00***	122.92±3.13$^{***\phi\phi\phi}$	120.83±4.17$^{***\phi\phi\phi}$	118.75±3.13$^{***\phi\phi\phi}$
36	94.79±1.56$^{\phi\phi\phi}$	90.62±1.56$^{\phi\phi\phi}$	91.67±00$^{\phi\phi\phi}$	220.83±00***	114.58±2.08$^{*\phi\phi\phi}$	113.54±1.56$^{*\phi\phi\phi}$	110.42±2.08$^{\phi\phi\phi}$

Values are expressed as mean ± SEM; ***p < 0.001 compared with the NaCl 0.9% control group; $^{\phi\phi\phi}$p<0.001 compared with the Alloxan group. With : *NaCl : NaCl 0.9% ; Lm5 : Lm 5 mg/kg/day ; Lm25 : Lm 25 mg/kg/day; Allox: Alloxan 150 mg/kg; Allox+Glib: Alloxan 150 mg/kg+ Glibenclamide 5 mg/kg/day ; Allox+Lm5 : Alloxan 150 mg/kg+Lm 5 mg/kg/day; Allox+Lm25 : Alloxan 150 mg/kg+Lm 25 mg/kg/day*

Table III: Effect of NaCl 0.9%, Lm extract of *Lannea microcarpa*, Glib, and Allox on animals' water feed intake during the experiment (n = 6).

	Feed consumption during the various treatments (g/Rat)						
	NaCl	**Lm5**	**Lm25**	**Allox**	**Glib5**	**Allox +Lm5**	**Allox +Lm25**
J4	19.25±0.56$^{\phi\phi\phi}$	18.37±0.92$^{\phi\phi\phi}$	18.14±0.44$^{\phi\phi\phi}$	26.64±0.25***	25.90±0.78***	26.49±1.14***	26.37±1.93***
J8	19.88±0.65$^{\phi\phi\phi}$	19.48±1.64$^{\phi\phi\phi}$	18.96±0.44$^{\phi\phi\phi}$	34.58±0.71***	35.71±1.23***	35.24±1.57***	34.08±2.59***
J12	20.13±0.61$^{\phi\phi\phi}$	19.57±1.21$^{\phi\phi\phi}$	19.19±0.48$^{\phi\phi\phi}$	35.13±0.77***	30.29±1.22$^{\phi\phi}$***	29.71±1.32$^{\phi\phi}$***	29.06±2.21$^{\phi}$***
J16	20.96±0.71$^{\phi\phi\phi}$	19.64±0.63$^{\phi\phi\phi}$	20.14±0.51$^{\phi\phi\phi}$	35.60±1.02***	25.07±1.01$^{\phi\phi\phi}$***	24.61±1.05$^{\phi\phi\phi}$**	23.70±1.81$^{\phi\phi\phi}$
J20	20.96±0.70$^{\phi\phi\phi}$	20.44±1.38$^{\phi\phi\phi}$	20.13±0.49$^{\phi\phi\phi}$	34.29±1.09***	23.82±1.29$^{\phi\phi\phi}$*	24.17±1.16$^{\phi\phi\phi}$*	23.34±1.89$^{\phi\phi}$
J24	21.46±0.66$^{\phi\phi\phi}$	20.60±1.37$^{\phi\phi\phi}$	20.53±0.49$^{\phi\phi\phi}$	33.75±1.02***	22.51±0.87$^{\phi\phi\phi}$*	22.25±1.15$^{\phi\phi\phi}$	21.21±1.80$^{\phi\phi\phi}$
J28	21.92±0.70$^{\phi\phi\phi}$	21.08±1.02$^{\phi\phi\phi}$	21.24±0.54$^{\phi\phi\phi}$	33.40±0.88***	21.94±0.86$^{\phi\phi\phi}$	21.79±1.08$^{\phi\phi\phi}$	20.83±1.69$^{\phi\phi\phi}$
J32	22.46±0.71$^{\phi\phi\phi}$	22.10±1.01$^{\phi\phi\phi}$	21.66±0.54$^{\phi\phi\phi}$	33.58±0.82***	22.54±1.01$^{\phi\phi\phi}$	21.25±0.98$^{\phi\phi\phi}$	20.28±1.57$^{\phi\phi\phi}$
J36	23.00±0.70$^{\phi\phi\phi}$	22.97±1.62$^{\phi\phi\phi}$	22.18±0.59$^{\phi\phi\phi}$	32.81±0.85***	21.94±1.45$^{\phi\phi\phi}$	21.52±1.39$^{\phi\phi\phi}$	20.12±1.56$^{\phi\phi\phi}$

Values are expressed as mean ± SEM; ***p < 0.001 compared with the NaCl 0.9% control group; $^{\phi\phi\phi}$p<0.001 compared with the Alloxan group. With : *NaCl : NaCl 0.9% ; Lm5 : Lm 5 mg/kg/day ; Lm25 : Lm 25 mg/kg/day; Allox: Alloxan 150 mg/kg; Allox+Glib: Alloxan 150 mg/kg+ Glibenclamide 5 mg/kg/day ; Allox+Lm5 : Alloxan 150 mg/kg+Lm 5 mg/kg/day; Allox+Lm25 : Alloxan 150 mg/kg+Lm 25 mg/kg/day*

Table IV: Effect of the Lm extract of *Lannea microcarpa* on liver lipid parameters in treated rats

Biochemical parameters analyzed at the end of treatment with Lm extract							
Parameters	**NaCl**	**Lm5**	**Lm25**	**Allox**	**Allox +Glib**	**Allox+Lm5**	**Allox+Lm25**
CT	1.31±0.27	1.45±0.22	1.48±0.25	1.30±0.26	1.24±0.10	1.72±0.18	0.96±0.09
HDL	0.37±0.06	0.55±0.11	0.47±0.07	0.48±0.09	0.49±0.06	0.53±0.07	0.56±0.09
TG	0.23±0.05	0.24±0.14	0.28±0.13	0.32±0.09	0.33±0.06	0.33±0.13	0.27±0.03
LDL	0.82±0.31	0.77±0.22	0.86±0.29	0.66±0.23	0.57±0.14	1.02±0.25	0.26±0.07

With : NaCl : NaCl 0.9% ;Lm5 : Lm 5 mg/kg/day ; Lm25 : Lm 25 mg/kg/day; Allox: Alloxan 150 mg/kg; Allox+Glib: Alloxan 150 mg/kg+ Glibenclamide 5 mg/kg/day ; Allox+Lm5 : Alloxan 150 mg/kg+Lm 5 mg/kg/day; Allox+Lm25 : Alloxan 150 mg/kg+Lm 25 mg/kg/day

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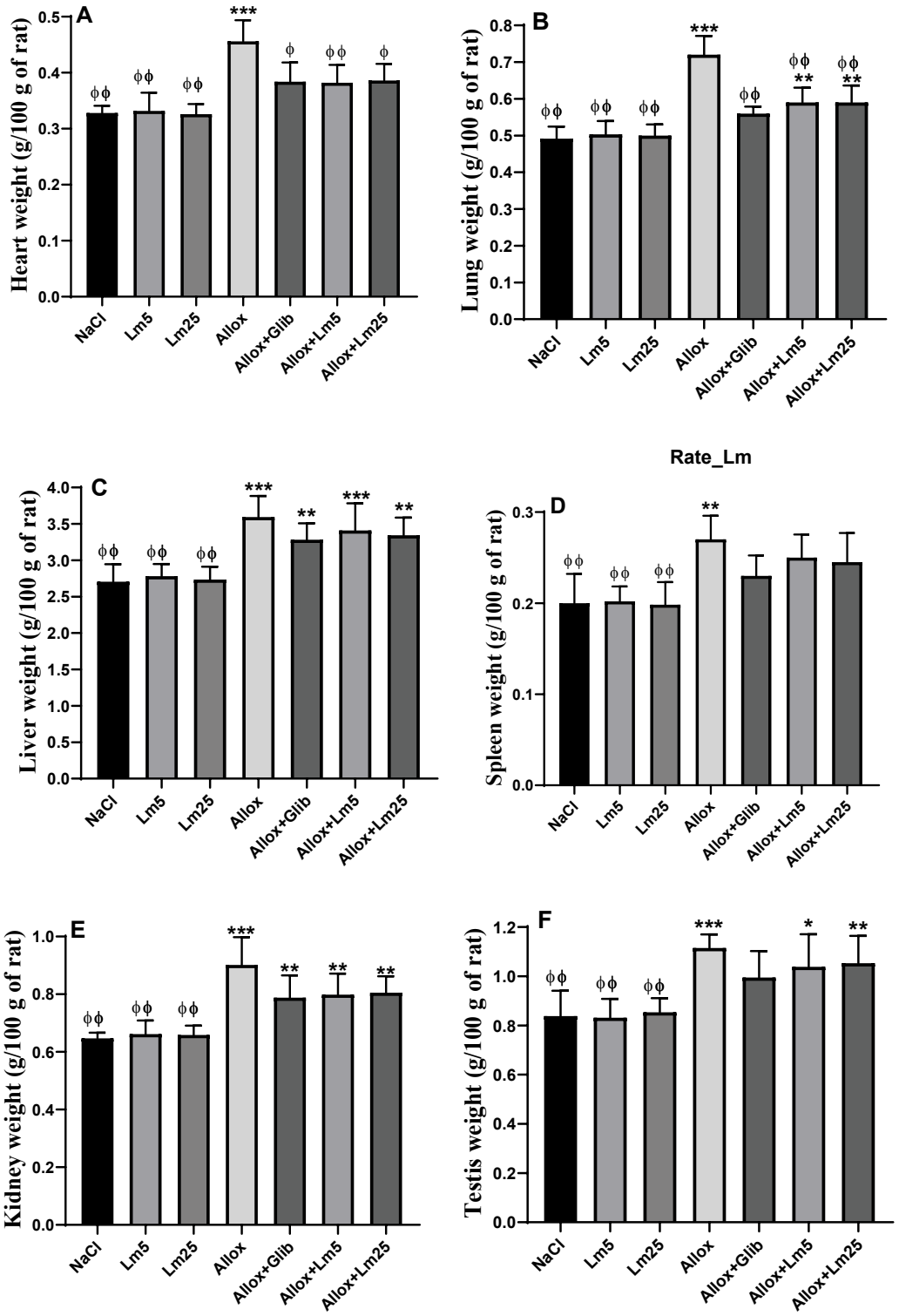

Figure 7: Effect of NaCl 0.9%, Lm extract of *Lannea microcarpa*, Glibenclamide, and Allox on mean organ weights of rats, A: Heart; B: Lungs; C: Liver; D: Spleen; E: Kidneys; F: Testes (n = 6). Values are expressed as mean ± SEM; ***p < 0.001 compared with the NaCl 0.9% control group; ϕϕϕp<0.001 compared with the Allox group. With: *NaCl : NaCl 0.9% ;Lm5 : Lm 5 mg/kg/day ; Lm25 : Lm 25 mg/kg/day; Allox: Alloxan 150 mg/kg; Allox+Glib: Alloxan 150 mg/kg+ Glibenclamide 5 mg/kg/day ; Allox+Lm5 : Alloxan 150 mg/kg+Lm 5 mg/kg/day; Allox+Lm25 : Alloxan 150 mg/kg+Lm 25 mg/kg/day*.

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Discussion

Diabetes is a serious disease characterized by high blood glucose levels, which, if left untreated, can lead to death in many cases [25, 26]. In addition, for its management, α-glucosidase inhibitors, SGLT-2 cotransporter inhibitors, DPP-IV and pancreatic GLP-1 receptor inhibitors, metformin, meglitinide analogs, and sulfonylureas are used [27–30]. However, in recent times, many diabetic patients are experiencing side effects and drug resistance followed by insulin resistance manifesting as type 2 diabetes [26]. Conventional drug therapy with effective anti-diabetic properties should, therefore, be explored. Thus, many folk medicinal plants from Africa, especially Burkina Faso, are traditionally used as effective anti-diabetic agents in treating or preventing diabetes [31]. The search for phytochemicals in the extract also enabled us to establish its anti-diabetic effect. It was, therefore, of interest to experimentally evaluate the antihyperglycemic properties of certain medicinal plants traditionally used to prevent or combat diabetes. Indeed, *L. microcarpa*, used in folk medicine, has never been studied for this purpose. Thus, the present study is the first to show the antihyperglycemic and hypoglycemic effects of the Lm extract of *L. microcarpa* trunk bark in alloxan-induced diabetic rats *in vivo.* Alloxan induces diabetes via ROS, which leads to rapid destruction of pancreatic beta cells, causing hyperglycemia. Hyperglycemia, in turn, increases the generation of free radicals via glucose auto-oxidation [14, 32]. The study's results revealed that daily doses of Lm5 and Lm25 for 4 days of treatment produced significant reductions ($P<0.05$) in mean blood glucose levels compared with diabetic control. This reduction in hyperglycemia was almost complete compared with blood glucose levels in healthy rats (NaCl 0.9%). The effect of the extract at both doses was comparable to that of glibenclamide (5 mg/kg/day). This finding suggests that the extract may act on the same pharmacological targets as the reference substance and could be a candidate for developing an anti-diabetic drug. An explanation could be the presence of antioxidants in the plant extract reported in a previous study [14, 16]. Antioxidants are protective agents that inactivate the ROS that cause cell damage. Work has reported that the antioxidant activity of hypoglycemic plant extracts may represent a protective mechanism against ROS associated with chronic hyperglycemia and diabetic complications such as microvascular and macrovascular conditions [14]. Interestingly, Lm extract contains flavonoids, coumarins, saponosides, triterpenic steroids, and tannins, which have antioxidant activity [16] and are thought to have an anti-hyperglycemic effect [33, 34]. This antihyperglycemic effect of Lm extract could be explained by its inhibition of hepatic glycogenolysis and, to a certain extent, gluconeogenesis. Indeed, studies have shown that stimulation of glycogenolysis leads to blood hyperglycemia [35, 36]. In addition, the anti-diabetic effects of Lm5 and Lm25 could be explained by an improvement in the activity of pancreatic beta cells, with an insulin-like effect similar to that of metformin in diabetics [37, 38]. The extract may also inhibit α-glucosidase, the SGLT-2 cotransporter, DPP-IV, and the pancreatic GLP-1 receptor. Thus, Lm5 and Lm25 could act on each cellular glucose signaling pathway in pancreatic beta cells, such as blocking direct glucose release or closing ATP-dependent potassium channels, reducing intracellular calcium levels, inhibiting the exocytosis mechanism, etc. [39]. Moreover, the administration of *L. microcarpa* extract to diabetic animals showed a significant improvement in the profile of physiological markers regarding hyperglycemia, namely weight loss and increased water and food intake. In fact, the effect of the extract was manifested by a reduction in the weight loss of treated diabetic rats and a decrease in water and food intake. Daily administration of Lm5, Lm25, or glibenclamide led to a progressive weight gain in the animals from day 12 of treatment up to the end of the study. These results corroborate other authors showing that many plant extracts with anti-diabetic properties improve animal weight loss [40–42]. The extract also had no anorexic, hyperhydration, or overhydration (hyponatremia) effects. In fact, the presence of saponosides, polyphenols, flavonoids, tannins, and coumarins in Lm extract is thought to be responsible for the antihyperglycemic effect, significantly reducing serum glucose, which has previously been validated in alloxan-induced diabetic models [26]. Studies have shown that the Lannea genus, *Lannea edulis*, possesses anti-diabetic properties through the inhibition of alpha-amylase [14]. In addition, Lm extract has already been shown to have vasorelaxant properties [15] and is, therefore, one of the antidiabetic pharmacological targets. Interestingly, Lm5 and Lm25 do not induce hypoglycemic effects in healthy rats. This has the advantage of avoiding serious side effects when preventing or treating moderate hyperglycemia. Indeed, authors have reported that hypoglycemia is the most important complication of insulin therapy in diabetes, particularly type 2 diabetes [43–45]. Moreover, the therapeutic doses of Lm extract are very low compared with the high dose of 1000 mg/kg/day evaluated during 4-week oral subacute toxicity, which showed no toxicological symptoms [46]. Analysis of the relative weights of noble organs such as the heart, lungs, liver, spleen, kidneys, and testes showed hypertrophy of the latter only in diabetics (Allox group). This organ hypertrophy was slightly corrected by administering Lm5, Lm25, and Glib. Indeed, previous studies have shown that alloxan-induced diabetes leads to hypertrophy of the noble organs. These results align with previous studies showing alloxan-induced tissue damage in these organs in diabetic animals [47–49]. In addition, induction of diabetes by alloxan did

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not significantly alter the lipid profile of liver function in diabetic rats (total cholesterol, triglyceride, HDL, and LDL) compared with healthy control rats (NaCl 0.9% group). Thus, Lm extract had no particular effect on diabetic rats. However, it is known that the onset of diabetes is associated with a drop in high-density lipoprotein-cholesterol (HDL-c) levels and a drastic increase in triglyceride and low-density lipoprotein-cholesterol (LDL-c) levels, which are responsible for atherosclerosis in the vessels [50–52]. Further studies may clarify this point.

Phytochemical studies using HPLC-MS have enabled us to provisionally identify compounds of pharmacological interest that could contribute to understanding the anti-diabetic or hypoglycemic effects observed during the experiment. Indeed, dihydroquercetin and kaempferol are flavones whose antioxidant, anti-inflammatory, and antifibrotic properties have been widely documented. Vladimirov et *al*. have demonstrated that dihydroquercetin can improve microcirculation by reducing cholesterol esterification in hepatocytes and triglyceride synthesis [53]. Moreover, as an isomer of quercetin, this compound acts on several target receptors involved in diabetes. For example, dihydroquercetin has a cardioprotective effect in diabetic patients by inhibiting NAPDH oxidase and angiotensin II production by stimulating the JAK2/STAT3 receptor [54]. In addition, authors have reported that quercetin potentiates the effect of metformin. This synergistic effect between quercetin and metformin would reverse persistent hyperglycemia and effectively protect the endothelium through modulation of endothelial NOS expression and VCAM-1 receptor [55]. As for kaempferol, this natural compound is considered an insulin promoter. This is because kaempferol can activate the mitochondrial Ca^{2+} monoporter, modulating insulin release and glycogenesis [56]. In addition, authors have demonstrated that kaempferol catalyzes the production of glucagon-like peptide 1 (GLP-1), enabling plasma insulin concentrations to be adjusted by modulation of chemical mediators, including Ca^{2+} and cAMP [56, 57]. The hypoglycemic effect of kaempferol has also been shown to regulate plasma glucose-6-phosphatase (G6PD) levels and increase glucokinase, a promoter of glycogen synthesis [58]. Kaempferol exerts a dual action in the liver, restoring the hexokinase pathway and inhibiting gluconeogenesis by inactivating pyruvate carboxylase [56]. HPLC-MS analysis revealed the presence of hydroxycinnamic acid derivatives, including 3 caffeoylquinic acid, commonly known as neochlorogenic acid. Previous work has shown that chlorogenic acid derivatives can improve physiological parameters during diabetes by exerting a hypoglycemic, hypolipidemic, and antioxidant effect. [59]. Authors have reported hypoglycemia following administration of 5 mg/kg/day of chlorogenic acid to diabetic rats [60]. Phytochemical analysis has also identified resveratrol and hesperetin derivatives whose anti-diabetic effects have been documented in the literature. These compounds act through various metabolic pathways to establish their anti-diabetic activity. They modulate the biosynthesis or release of several proteins or enzymes, including protein kinase B -PKB- (Akt), insulin receptor 1 (IRS-1), glycogen synthase kinase 3 (GSK3β), glyoxalase 1 (Glo1), thioredoxin interacting protein (TXNIP) and TNF-α [61–63].

Conclusion

The study demonstrated that the Lm extract of *L. macrocarpa* trunk bark (5 mg/kg/day and 25 mg/kg/day) significantly reduced blood glucose levels in alloxan-induced diabetic rats, showing a natural potential in diabetes management. The extract has the ability to counteract the pathophysiological effects of diabetes by increasing the weight of diabetic rats compared to untreated diabetic rats. It normalizes the hyper-consumption of water and food and the hypertrophy of noble organs induced by diabetes. *Lannea microcarpa* extract is also safe to use as it does not induce hypoglycemic effects or weight loss in healthy rats at the therapeutic doses used in treatment. Therefore, the extract's anti-diabetic properties are linked to various bioactive compounds, notably triterpenic sterols, anthocyanins, and phenolic compounds. Also, flavonols, isoflavonoids, and hydrocinnamic acid derivatives identified in the extract demonstrate its anti-diabetic potential. Finally, these results may justify further research into the Lm extract of *Lannea microcarpa* trunk bark as a natural source of new anti-diabetic therapies.

Competing Interests

The authors declare that there is no conflict of interest to disclose regarding the publication of this paper.

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