Magnesium Enhances the Hepatorenal Protective Effects of *Lippia multiflora* Aqueous Leaves Extract in Streptozotocin-Diabetic Rats

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Abstract

Purpose: This study was conducted in order to evaluate the antidiabetic effects of the aqueous extract of *Lippia multiflora* supplemented with magnesium on some biochemical markers of the kidneys and liver in type 2 diabetic rats. **Method:** 7 groups of 4 STZ-diabetic rats received separately orally Glucophage® (Glu 10 mg/kg), the plant extract (LiMAE 200 - 600 mg/kg) and the plant extract supplemented with magnesium (LiMAE-Mg 200 - 600 mg/kg). After a daily treatment of 21 days, serum biochemical parameters were assayed in 16 hr-fasted rats. **Results:** Diabetes caused a significant ($p < 0.0001$) elevation of urea, creatinine, ALT and AST. Treatment of diabetic rats with plant extracts (LiMAE and LiMAE-Mg) and Glucophage significantly restored levels of these biochemical markers at $p < 0.0001$. However, the restoration induced by LiMAE-Mg was greater than those of LiMAE and Glucocophage, a reference antidiabetic. **Conclusion:** The addition of magnesium to the extract of *Lippia multiflora* caused a greater reduction in the levels of urea, creatinine, ALT and AST increased in STZ-diabetic rats. Magnesium would therefore enhance the nephroprotective and hepatoprotective effects of *Lippia multiflora* in diabetic rats.

Keywords

Lippia multiflora, Diabetes, Streptozotocin, Nephroprotective, Hepatoprotective

1. Introduction

Diabetes is a chronic metabolic disease caused by an inability of the body to produce enough insulin (type 1) or to use it effectively (type 2). It is a non-

communicable disease characterized either by chronic hyperglycemia or by fasting blood glucose above 1.26 g/l. Diabetes, because of its manifestation and its treatment, constitutes a real public health problem. Its expensive and lifelong treatment leads poor populations in developing countries to use medicinal plants. In view of the controversies on the efficacy and safety of the use of medicinal plants, studies have been undertaken on *Lippia multiflora*, a plant reputed to be antidiabetic [1].

Several studies have been carried out on the effects of *Lippia multiflora* in diabetic rats. They revealed on the one hand the non-toxicity of *Lippia multiflora* aqueous leaves extract [2] and on the other hand its antidiabetic properties. *Lippia multiflora* aqueous extract (LiMAE) corrected several disturbances caused by diabetes in Wistar rats. This antidiabetic activity of LiMAE would, moreover, be reinforced by magnesium. Indeed, the aqueous extract of *Lippia multiflora* supplemented with magnesium (LiMAE-Mg) compared to LiMAE resulted in a greater restoration of the levels of glycemia, insulinemia, glycosylated hemoglobin, lipid profile and cardiovascular parameters in STZ-diabetic rats [3]. Magnesium would also potentiate the antioxidant activity of LiMAE [4]. These results are in agreement with those of previous work which demonstrated that magnesium would positively increase the effects of certain antidiabetic substances [5] [6] [7].

The results of this work, although interesting, are not sufficient to fully demonstrate the antidiabetic action of *Lippia multiflora* aqueous leaves extract supplemented with magnesium. Indeed, diabetes is associated with many complications including not only endocrine and cardiovascular disorders but also dysfunctions of several vital organs. Persistent hyperglycemia over time can affect almost any organ, especially the kidneys and liver [8].

And it is in this sense that the present research was carried out in order to evaluate the effects of *Lippia multiflora* aqueous leaves extract supplemented with magnesium on some biochemical markers of kidney and liver functionalities in streptozotocin-diabetic rats.

2. Materials and Methods

2.1. Plant Material and Extracts

Fresh leaves of *Lippia multiflora* (Verbenaceae) were harvested in February 2018 in Assouvoué, village of Toumodi Commune (Région du Bélier, Côte d'Ivoire). The fresh leaves were identified and authenticated by a Botany expert, Dr ASSI Rose-Monde of the "Centre National de Floristique", UFR-Biosciences, Félix Houphouët-Boigny University (Abidjan, Côte d'Ivoire).

The plant aqueous extract was obtained according to the method used by Allo *et al.* [3]. The fresh leaves were washed and dried at room temperature (28°C ± 2°C). Dried leaves were pulverized to powder with the use of a laboratory blender-About 100 g of powder were macerated during 24 hrs in distilled water (1 L), thereafter filtered. An oven at a temperature of 50°C was used to concentrate the

filtrate. And the concentrated extracts obtained (*Lippia multiflora* aqueous leaves extract: LiMAE) was stored at 4˚C until experiments. LiMAE was supplemented with magnesium (1 g per 9 g LiMAE) to give the supplemented *Lippia multiflora* aqueous extract (LiMAE-Mg).

2.2. Animals and Ethics

Wistar rats (*Rattus norvegicus*) weighing 200 - 250 g and 8 - 12 weeks old were used. These animals were provided by the Pasteur Institute of Côte d'Ivoire (IPCI). They were acclimatized for 2 weeks before being used for experiments. Animals were housed and maintained under standard laboratory conditions (temperature 25˚C ± 2˚C) with dark and light cycle (12/12h). They were allowed free access to standard dry pellet diet and water *ad libitum*. Rats were treated according to good laboratory practices [9]. The experimental protocols were conducted in accordance with the protocols for the protection of experimental animals of the European Council on Legislation 2012/707 [10].

2.3. Chemicals Used

Streptozotocin (STZ 500 mg, Sigma-Adrich, USA), D(+) glucose monohydrate (Riedel-de Haën®, Germany), 0.1 M citrate buffer pH 4.5 (Merk®, USA), Nicotinamide (Sigma-Aldrich®, USA), Metformin hydrochloride (Glucophage® 10 mg, Sanofi-Aventis, France), Magnesium chloride crystals (ABCO®, Delbet, France) and Isoflurane (Forène®, Roche, France) were used. And Commercials Kit obtained from Spinreact (Spin).

2.4. Experimental Induction of Diabetes

The method used to induce type 2 diabetes in rats is similar to those of previous works [3] [4] [11] [12]. Fifteen minutes after receiving a single dose of streptozotocin (STZ, 65 mg/kg), 16 hr-fasted rats were treated with nicotinamide (230 mg/kg). STZ which was freshly prepared in citrate buffer solution (0.1 M, pH = 4.5) and nicotinamide were administered intraperitoneally. From D14 to D21, augmented levels of blood glucose (2 - 3 g/L), urea, creatinine, AST and ALT in 16 hr-fasted rats and body weight decrease confirmed the development of the diabetes.

2.5. Experimental Design

The experimental protocol is that described by Allo *et al.* (2022) [3] and Konan *et al.* (2023) [4]. Four healthy rats (Group 1) and 32 STZ-diabetic rats divided into 8 groups of 4 animals (Groups 2-9) were used. Group 1 (HeR: healthy rats) and Group 2 (uDR: untreated-diabetic rats) received distilled water. Group 3 received Glucophage (Glu 10 mg/kg). Groups 4, 5, 6 were treated with LiMAE at 200, 400 and 600 mg/kg respectively while Groups 7, 8 and 9 received LiMAE-Mg at 200, 400 and 600 mg/kg respectively. Drugs were administered orally for 21 days. And all animals had free access to water and normal diet during the expe-

rimentation. Rats were weighed at the start and end of the phase. Intermediate weighings at regular intervals of 2 days were also made. After 21 days administration of drugs studied to the experimental animals, they were starved overnight, anaesthetized with Isoflurane (Forene®) and sacrificed. A thoracotomy was performed. Blood samples were collected from the animals through cardiac puncture.

Blood samples collected in non-heparinized tubes were allowed to clot for about 15 min and centrifuged at 3000 rpm for 5 min. Serum was separated from the clot with pasteur pipette and dispensed into clean tube for the measurement of the biochemical indices. Analysis of the selected serum biochemical indices were carried out on each sample. Parameters were measured using Chemistry Analyzer (HITACHI 704R® auto-analyser). The serum biomarkers measured were urea and creatinine for the kidney and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) for the liver. Indeed, these parameters have been measured by several authors to study the functions of the kidney and liver [13] [14] [15].

2.6. Data Analysis

All the data were expressed as Mean ± Standard Error of Means (SEM). Statistical analyses were performed by one way analysis of variance (ANOVA) and differences between means were determined by Turkey's Multiple Comparison test using Graph Pad Prism 7.0 program (Microsoft, San Diego California, USA). A value of $p < 0.05$ was considered significant.

3. Results

3.1. Effects of Studied Drugs on Biochemical Markers of Kidney Functionality

A significant elevation ($p < 0.05$) of the urea level at 1.00 ± 0.02 g/L was measured in untreated-diabetic rats (uDR) against 0.49 ± 0.02 g/L for healthy rats (HeR), an increase of 51% (Figure 1). At a dose of 200 mg/kg, the extracts (LiMAE and LiMAE-Mg) reduced the urea level to 0.87 ± 0.05 g/L and to 0.77 ± 0.02 g/L giving respective reductions of 13% and 23% compared to that of uDR. LiMAE and LiMAE-Mg at a dose of 400 mg/kg caused a respective decrease of urea levels to 0.72 ± 0.03 g/L and 0.66 ± 0.02 g/L corresponding to respective reductions of 28% and 34% compared to that of uDR. At a dose of 600 mg/kg, LiMAE and LiMAE-Mg caused a decrease in urea levels in diabetic rats with respective values of 0.59 ± 0.02 g/L and 0.57 ± 0.05 mg/L. These values correspond respectively to a reduction of 41% and 43% compared to that of uDR. With Gluco 10 mg/kg, a urea value of 0.73 ± 0.02 g/L was measured. Treatment with Gluco 10 mg/kg therefore resulted in a 27% decrease in urea in treated diabetic rats compared to uDR.

Induction of diabetes also caused a significant elevation in creatinine level (Figure 2). The rate was 60.89 ± 2.25 mg/L in uDR versus 13.02 ± 1.56 mg/L for
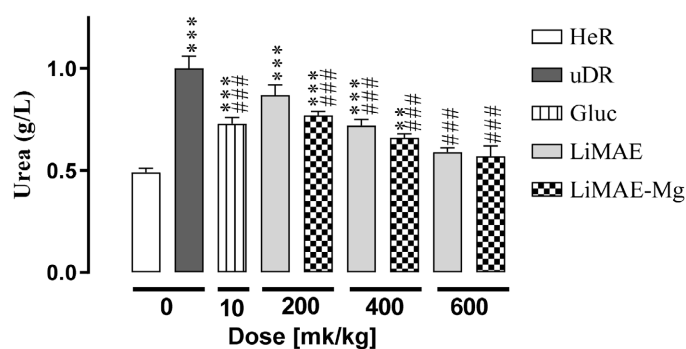
Figure 1. Effects of drugs on urea in STZ-diabetic rats. M ± SEM; n = 4; ***$p < 0.0001$, **$p < 0.001$: significant difference with healthy rats (HeR); ###$p < 0.0001$: significant difference with untreated diabetic rats (uDR); STZ: streptozotocin; Gluc: Glucophage; LiMAE: *Lippia multiflora* leaves aqueous extract; LiMAE-Mg: *Lippia multiflora* leaves aqueous extract supplemented with magnesium.
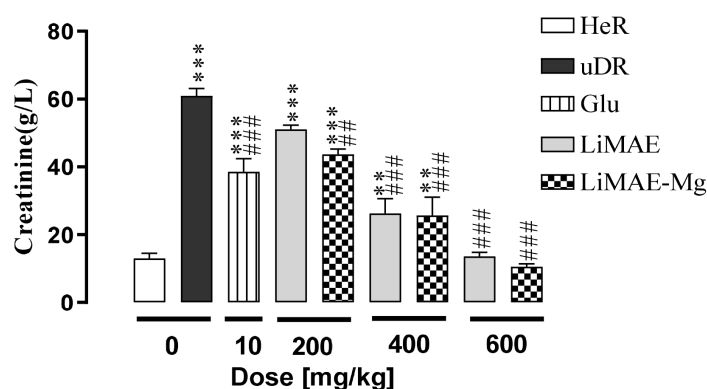
Figure 2. Effects of drugs on creatinine in STZ-diabetic rats. M ± SEM; n = 4; ***$p < 0.0001$, **$p < 0.001$: significant difference with healthy rats (HeR); ###$p < 0.0001$: significant difference with untreated diabetic rats (uDR); STZ: streptozotocin; Glu: Glucophage; LiMAE: *Lippia multiflora* leaves aqueous extract; LiMAE-Mg: *Lippia multiflora* leaves aqueous extract supplemented with magnesium.

HeR. Creatinine was evaluated at 38.52 ± 3.89 g/L in diabetics treated with Gluc 10 mg/kg. The reduction caused by the reference antidiabetic substance was 36.73% compared to untreated diabetic rats. At a dose of 200 mg/kg, LiMAE and LiMAE-Mg caused a respective reduction of 51.08 ± 1.28 g/L and 43.63 ± 1.64 g/L, *i.e.* a reduction of 16.11% and 28.34% compared to uDR. At 400 mg/kg, levels of 26.25 ± 4.37 g/L (LiMAE) and 25.68 ± 5.37 mg/L (LiMAE-Mg) were recorded giving respective reductions of 56.88% and 57.80%. Aqueous extracts administered at 600 mg/kg reduced creatinine levels to 13.62 ± 1.16 g/L (LiMAE) and 10.53 ± 0.92 g/L (LiMAE-Mg) in diabetic rats. This equates to a reduction of 77.63% and 82.70% compared to uDR.

3.2. Effects of Studied Drugs on Biochemical Markers of Liver Functionality

Diabetes increased AST transaminase activity significantly at $p < 0.05$ in uDR (186.36 ± 2.17 IU/L) compared to that in HeR (154.81 ± 3.59 IU/L). This in-

crease was estimated at 20.67% (Figure 3). Administration of LiMAE and Li-MAE-Mg caused a reduction in AST activity in diabetic rats. Thus, 181.66 ± 0.86 IU/L, 175.52 ± 1.72 IU/L and 164.24 ± 3.09 IU/L were measured with LIMAE at 200, 400, 600 mg/kg respectively. Compared to uDR, these are respective decreases in AST activity of 2.52%, 5.81% and 11.86%. At these same doses, corresponding greater decreases of 177.14 ± 3.17 IU/L, 170.60 ± 1.80 IU/L and 155.35 ± 4.18 IU/L were observed in the diabetic rats which had received Li-MAE-Mg. This corresponded to respective decreases of 4.94%, 8.45% and 16.63% compared to the value recorded in uDR. The reference antidiabetic substance, Glucophage at 10 mg/kg, caused an 8.84% decrease in AST activity in uDR.

Regarding ALT transaminase activity, it also increased with diabetes. It went from 55.17 ± 1.99 IU/L (HeR) to 91.28 ± 1.18 IU/L (uDR), an increase of 65.45%. *Lippia multiflora* aqueous extracts (LiMAE and LiMAE-Mg) and Glucophage, on the contrary, induced a decrease in ALT activity in diabetic rats (Figure 4). Values of 81.97 ± 1.89 IU/L, 72.74 ± 2.64 IU/L and 61.67 ± 2.66 IU/L corresponding to reductions in AST activity of 10%, 20%, 20.31% and 32.43% were recorded with LiMAE at 200, 400 and 600 mg/kg respectively in comparison to uDR. LiMAE-Mg showed statistically greater reductions in ALT activity in diabetic rats than LiMAE. In diabetic rats treated with LiMAE-Mg, recorded ALT activity decreased from 83.54 ± 2.31 IU/L (200 mg/kg) to 66.38 ± 3.57 IU/L (600 mg/kg). Thus, LiMAE-Mg (200 - 600 mg/kg) reduced decreases in ALT activity from 8.47% to 27.27%. As for Glucophage at 10 mg/kg, it caused a reduction in ALT activity of 15.83% in diabetic rats.

4. Discussion

The induction of diabetes caused an increase in serum levels of AST, ALT, urea and creatinine in animals as revealed by numerous works [3] [4] [11] [16]. In general, an increase in transaminases (AST and ALT) in the blood implies liver
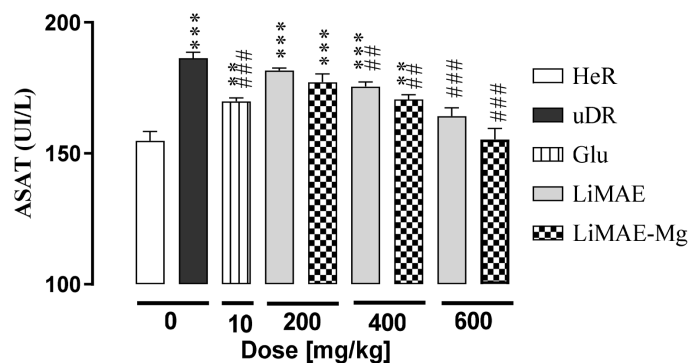
Figure 3. Effects of drugs on AST in STZ-diabetic rats. M ± SEM; n = 4; ***p < 0.0001, **p < 0.001: significant difference with healthy rats (HeR); ###*p* < 0.0001, ##*p* < 0.001: significant difference with untreated diabetic rats (uDR); AST: Aspartate aminotransferase (AST); STZ: streptozotocin; Glu: Glucophage; LiMAE: *Lippia multiflora* leaves aqueous extract; LiMAE-Mg: *Lippia multiflora* leaves aqueous extract supplemented with magnesium.
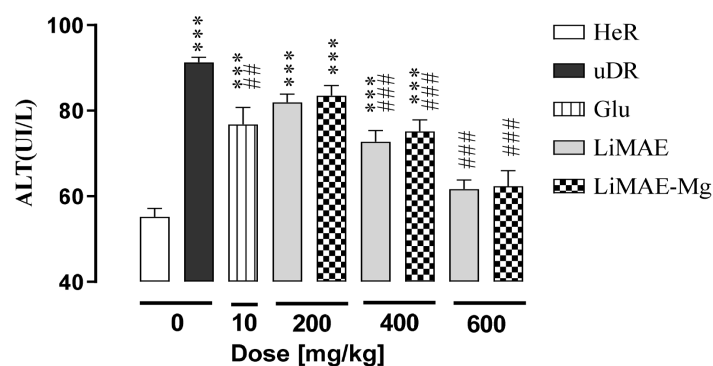
Figure 4. Effects of drugs on ALT in STZ-diabetic rats. M ± SEM; n = 4; ***$p < 0.0001$, **$p < 0.001$: significant difference with healthy rats (HeR); ###$p < 0.0001$, ##$p < 0.001$: significant difference with untreated diabetic rats (uDR); ALT: Alanine aminotransferase; STZ: streptozotocin; Glu: Glucophage; LiMAE: *Lippia multiflora* leaves aqueous extract; LiMAE-Mg: *Lippia multiflora* leaves aqueous extract supplemented with magnesium.

damage, while an increase in urea and creatinine levels indicates kidney damage [12] [17] [18]. This would mean that diabetes has caused damage to the organs such as the liver and kidneys, hence the increase in serum concentrations of these biomarkers [8] [19] [20]. Treatment of diabetic animals with *Lippia multiflora* aqueous extracts (LiMAE and LiMAE-Mg) significantly decreased serum levels of AST, ALT, urea and creatinine in a dose-dependent manner. The levels of the biomarkers studied were normalized in comparison to those of healthy rats. This suggests that *Lippia multiflora* aqueous extracts (LiMAE and LiMAE-Mg) could protect the liver and kidneys in diabetics. The effects of the aqueous extract of *Lippia multiflora* used alone (LiMAE) are similar to those described by previous works [15] [21] [22] [23] [24]. They have, in fact, shown the ability of plant extracts to improve liver function through a reduction in the ALT value and the AST value and also improve kidney function through a reduction in the value urea and creatinine [13] [18] [25] [26] [27]. These works demonstrated the dose-dependent hepatoprotective and nephroprotective activities of medicinal plants in diabetic rats [13] [28] [29].

Analysis of the results also showed that LiMAE-Mg or *Lippia multiflora* extract combined with magnesium induced greater reductions in serum concentrations of AST, ALT, urea and creatinine compared to LiMAE, the aqueous extract of *Lippia multiflora* used alone in diabetic rats. In other words, LiMAE-Mg led to a greater restoration of parameters disrupted by the occurrence of STZ-induced diabetes. This shows that magnesium enhanced the nephroprotective and hepatoprotective effects of *Lippia multiflora* in diabetic rats. These results are in agreement with those of previous works. Magnesium enhances the antidiabetic activity of *Lippia multiflora* aqueous extract on glycemia, lipid profile and cardiovascular parameters in STZ-diabetic rats [3]. Along the same lines, Konan *et al.* (2023) [4], for their part, demonstrated that magnesium enhances the antidiabetic activity of *Lippia multiflora* aqueous leaves extract on redox status in STZ-diabetic rats. The results obtained in the present study are also

corroborated by several previous works [30] [31] [32] [33]. These revealed that the potentiating effect of magnesium on the antidiabetic action of biological substances and in particular medicinal plant extracts [34] [35] [36] [37].

It therefore emerges from these observations that magnesium interacts positively with the secondary metabolites contained in *Lippia multiflora* aqueous leaves extract. These could include flavoids, alkaloids, tannins highlighted by various studies [2] [38] and whose hepatoprotective and nephroprotective actions have been demonstrated [16] [33] [39].

5. Conclusion

Lippia multiflora aqueous leaves extract supplemented with magnesium caused a greater reduction in the levels of kidney and liver biomarkers that were elevated in diabetic rats. Magnesium would therefore enhance the hepatoprotective and nephroprotective effects of *Lippia multiflora* aqueous extract. This provides scientific support for the use of medicinal plants such as *Lippia multflora* in the treatment of liver and kidney disorders caused by diabetes. Treatment of the diabetic rats with *Lippia multiflora* leaves extract associated with *magnesium* is more effective in the amelioration of diabetes and hepato-renal injuries in STZ induced diabetic male rat. And therefore, magnesium supplementation of *Lippia multiflora* aqueous extract could be an interesting alternative for the development of new products to treat diabetes.

Acknowledgements

Author's Contribution

All authors contributed equally in the study. They made substantial contributions to the design of the study, the collection of the data as well as the preparation and analysis of the data. They also drafted the manuscript and gave final approval for its submission to the journal for consideration of publication.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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