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Magnesium Enhances the Antidiabetic Activity of *Lippia multiflora* Aqueous Leaves Extract on Redox Status in Streptozotocin-diabetic Rats

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Abstract **Original Research Article**

***Objective*:** This study was conducted in order to evaluate the antioxidant effects of *Lippia multiflora* aqueous extract supplemented with magnesium in diabetic rats. ***Méthodes*:** 7 groups of 4 STZ-diabetic rats received separately the Glucophage® (Glu 10 mg/kg), the plant aqueous extract (LiMAE 200-600 mg/kg) and the plant aqueous extract supplemented with magnesium (LiMAE-Mg 200-600 mg/kg) in comparison to healthy rats and untreated diabetic rats. After 21 days of daily treatment, activities of enzymes-markers of oxidative stress were measured on kidney and pancreas samples. ***Results*:** The occurrence of diabetes induced a significant increase in MDA and a significant decrease in CAT, SOD and GSH in rats. Separate treatment of animals with LiMAE and LiMAE-Mg significantly restored at $p < 0.0001$ and in a dose-dependent manner the activities and levels of enzymes-markers of oxidative stress. This restoration was greater with LiMAE-Mg, the aqueous extract of *Lippia multiflora* supplemented with magnesium. LiMAE-Mg very significantly restored the studied parameters with measured values statistically close to normal. ***Conclusion*:** The results showed the antidiabetic potential of *Lippia multflora* extract supplemented with magnesium on oxidative stress.

Keywords: *Lippia multiflora*, oxidative stress, diabetes, Magnesium, rat.

INTRODUCTION

Oxidative stress is the term referring to disturbances in the balance between the formation of reactive oxygen species and the body's ability to neutralize their action by antioxidant systems. This imbalance can damage certain macromolecules (nucleic acids, lipids and proteins), leading to the appearance of various human diseases [1]. Antioxidants can be defined as any substance which, present at a low concentration relative to the oxidizable substrate, is capable of slowing down or inhibiting the oxidation of this substrate [2].

Many pathologies involving oxidative stress in their development, have been identified. In addition to cardiovascular diseases (oxidation of lipids) and cancer (DNA oxidation), diabetes (obesity, metabolic disorder) is certainly the case where notable advances have been made in recent years. Several mechanisms lead to an increase in oxidative stress and seem to be involved in the onset of diabetes complications [3].

Given the high cost of modern treatment of diabetes in Africa, patients resort to traditional medicine using plants known to be antidiabetic. These medicinal plants would also be important sources of antioxidants. It is in this context that an evaluation of the beneficial effects of *Lippia multiflora* was undertaken. *Lippia multflora* (Verbenaceae) is a plant commonly used to treat diabetes [4]. Previous works have shown an antidiabetic action of this plant on glycaemia, insulinaemia, glycated hemoglobin, lipid profile, glycid profifl and cardiovascular parameters in STZ-diabetic rats [5]. This antidiabetic action of the aqueous extract of *Lippia multiflora* leaves was potentiated by magnesium. This has been shown by greater antidiabetic effects obtained with the plant extract supplemented with magnesium [5].

The objective of the present study was to evaluate the activity of enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) in the presence of the

aqueous extract of *Lippia multiflora* leaves supplemented with with magnesium in type 2 diabetic rats.

MATERIALS AND METHODS

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 fresh leaves were washed and dried at room temperature (28 ± 2 °C).

The plant aqueous extract was obtained according to the method used by Allo et *al.*, [5]. The powder of dried leaves (100 g) was macerated during 24 hrs in distilled water (1L), thereafter filtered. An oven at a temperature of 50 °C was used to concentrate the filtrate. And the concentrated extracts obtained (*Lippia multiflora* leaves aqueous 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).

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). The experiments were carried out according to the standards of good laboratory practices [6, 7].

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), Isoflurane (Forène®, Roche, France) and Commercials Kit (Spinreact, Spin)were used.

Experimental induction of diabetes

The method used to induce type 2 diabetes in rats is similar to those of previous works [5, 8, 9]. 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 [5, 8, 9].

Study design

The experimental protocol is that described by Allo *et al*. [5]. 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. And all animals had free access to water and normal diet during the experimentation. After 21 days administration of drugs studied to the experimental animals, they were starved overnight, anaesthetized with Isoflurane and sacrificed. A median laparotomy was performed to remove the pancreas and kidneys from the animals for the evaluation of oxidative stress parameters.

Measurement of oxidative stress markers

Catalase assay

Catalase (CAT) reduces hydrogen peroxide (H_2O_2) to water (H_2O) and oxygen (O_2) [10]. In a test tube containing 0.1 mL of the organ homogenate was added 250 µL of phosphate buffer and 200 µL of hydrogen peroxide. Then 1 mL of the dichromate and acetic acid mixture was added to stop the reaction. Incubation was done in a bath at 100 °C for 10 min. The OD at 620 nm was read using a spectrophotometer.

Malonadehyde (MDA) assay

The assay is based on the formation in an acidic and hot medium (95 °C) between MDA and thiobarbituric acid (TBA) of a pink pigment absorbing at 532 nm, extractable by organic solvents such as butanol. The MDA level was evaluated using the method described by Yoshioka *et al.*, [11]. Protein precipitation was performed by adding 1.25 mL of trichloroacetic acid solution (20 %) to 0.25 mL of the organ homogenate. Subsequently, 0.5 mL of a solution of thiobarbituric acid (0.67 %) was added. After incubation in a water bath (95°C) for 30 min, the mixture was cooled rapidly. Finally, 4 mL of n-butanol was added. The mixture was vortexed and centrifuged at 2000rpm for 10 min. The OD values were read at 532 nm and the concentrations expressed in mmol/L were calculated using Beer Lambert's law:

DO = Ɛ* C * L C = DO/ Ɛ* C * L

with L = tank length

Superoxide dismutase (SOD) activity assay

SOD activity was measured by Nitro Blue Tetrazonium (NBT) test. NBT is reduced by NADPH in the presence of the superoxide anion (O_2-) and gives a dark purple chromophore [12]. While SOD eliminates the superoxide anion (O_2-), the intensity of the color of the chromophore is proportional to the activity of SOD in the medium. However, the activity of SOD was measured according to the following method. In a test tube were added 5 µL of the organ homogenate and 2 mL of the reaction mixture (2x10-5 M sodium cyanide; 1.76x10-4 M NBT solution; 6.6x10-3 M EDTA;

riboflavin 2x10-6 M; 10-2 M methionine and 3 mg of NADPH). Then the mixture obtained was irradiated with a 15 watt lamp for 10 min. Finally, the absorbance was measured at 560 nm. SOD activity values are expressed in IU.mg-1 of protein.

Glutathione peroxidase (GSH) assay

The method of Ellman [13] was used for the determination of the level of GSH. In 50 mL of 55% trichloroacetic acid (TCA), 1 g of fresh tissue (pancreas, kidney) was homogenized using a Dounce grinder. After centrifugation at 2000 rpm of the homogenate for 10 min, 50 µL of the supernatant was diluted in 10 mL of phosphate buffer (0.1 M, pH = 8). And 3 mL of the mixture was added in 20 µL of 2-nitrobenzeic acid (DTNB at 0.01 M). The absorbance was read at 412 nm against a blank prepared under the same conditions with TCA 55%.

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.

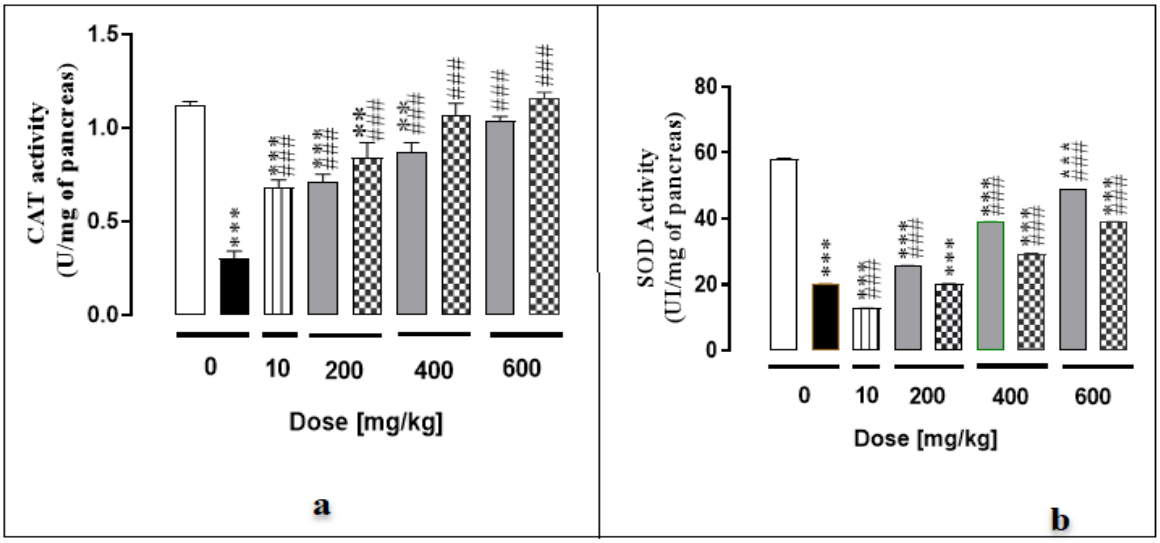
RESULTS

Effects of the substances studied on SOD, CAT and MDA at the level of the pancreas in diabetic rats

Induction of diabetes caused a decrease in activities of CAT and SOD as well as an increase of that of MDA compared to healthy animals (Fig 1).

Indeed, STZ significantly ($p < 0.05$) decreased CAT activity in diabetic rats from 1.12 ± 0.04 IU/g of pancreas to 0.30 ± 0.04 IU/ g of pancreas and from 58.28 ± 1.48 IU/g of pancreas to 20.19 ± 1.74 IU/g of pancreas for that of SOD compared to healthy rats. This corresponds to respective reductions of 73.21 % and 65.35 %. Regarding MDA, the induction of diabetes significantly increased its level from 0.61 ± 0.02 mmol/g of pancreas in healthy rats to 2.89 ± 0.04 mmol/g of pancreas in diabetic rats, an increase of 473.77 %. Treatment of diabetic rats with the LiMAE and LiMAE-Mg extracts significantly ($p < 0.05$) increased the activities of CAT and SOD compared to those of untreated diabetic rats. This increase in the activities of CAT and SOD was greater from the dose of 400 mg/kg. At this dose, LiMAE increased CAT activity by 290 % and SOD activity by 193.56 % in diabetic rats. Similarly, LiMAE-Mg increased CAT and SOD activities by 356.66% and 145.76%, respectively. At the 600 mg/kg, LiMAE and LiMAE-Mg significantly increased catalase activity by 346.66% and 386.66% respectively. In the same order, an increase of 243.73% and 193.21% was recorded for that of SOD

As for MDA, the treatment of diabetic rats with *Lippia multiflora* extracts (LiMAE and LiMAE-Mg) allowed a very significant reduction in its level, especially at a dose of 600 mg/kg. At this high dose, a reduction in the level of MDA of 69.20 % and 77.16% was measured respectively with LiMAE and LiMAE-Mg. The effect of Glucophage (10 mg/kg) was not significant at $p > 0.05$ on the activities of CAT, SOD and on the level of MDA during the treatment of diabetic rats.



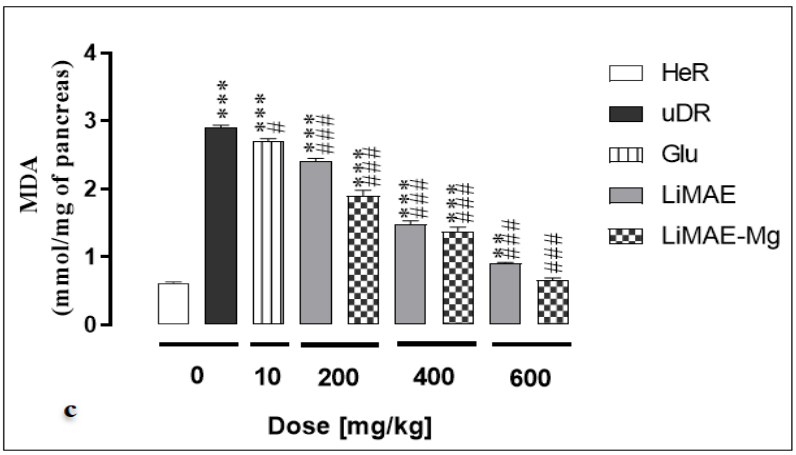


Figure 1: Effects of the substances studied on oxidative stress enzyme-markers in diabetic rats pancreas. ***a) Catalase (CAT), b) Superoxyde dismutase (SOD), c) Malonadehyde (MDA). m ± sem; n= 4; ***p <0,0001; **p <0,001 : significant difference with healthy rats (HeR); ###p < 0,0001; #p < 0,01: significant 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.***

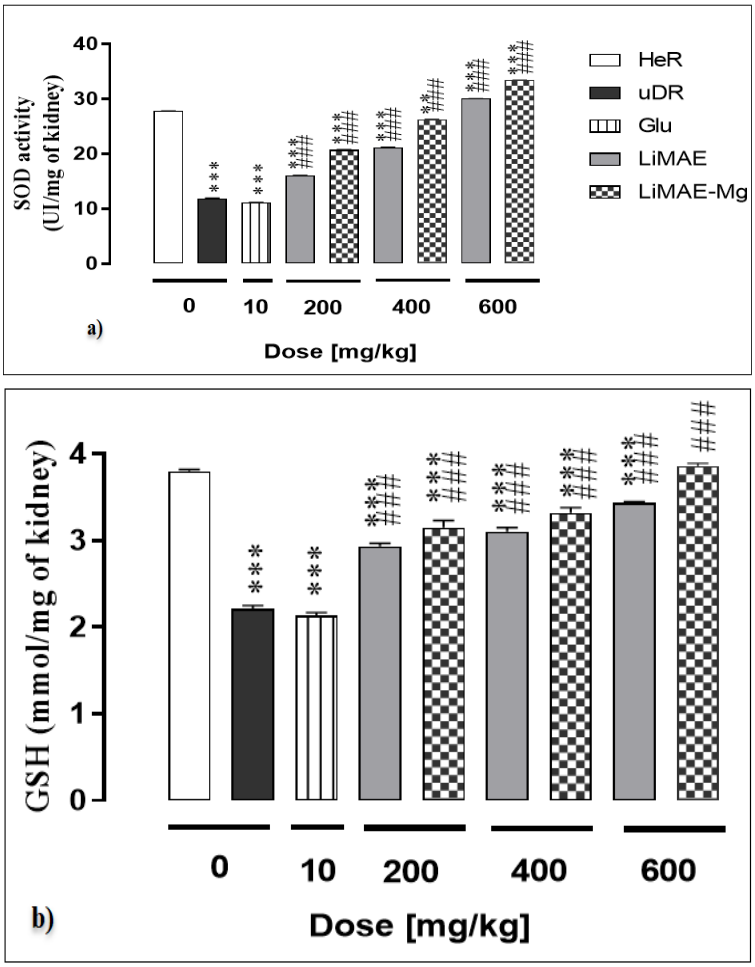


Figure 2: Effects of the substances studied on oxidative stress enzyme-markers in diabetic rats kidney. ***a) Superoxyde dismutase (SOD), b),* Glutathione peroxidase (GSH);** ***m ± sem; n= 4, ***p <0,0001 ; **p <0,001 : significant difference with healthy rats (HeR); ###p<0,0001 : significant difference 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.***

Effects of the substances studied on SOD and* GSH *at the level of kidney in diabetic rats

The effects of *Lippia multiflora* extracts (LiMAE and LiMAE-Mg) and Glucophage on the activities of SOD and GSH in the kidney are shown in figure 2. Induction of diabetes caused a significant decrease ($p < 0.0001$) in GSH and SOD activities in diabetic rats compared to healthy rats. With values of 27.79 ± 0.47 IU/g kidney (HeR) and 11.89 ± 0.79 IU/g of kidney (uDR), STZ induced a significant decrease of

SOD activity by 57.21 %. The level of GSH decreased from 3.80 ± 0.06 mmol/g of kidney (HeR) to 2.21 ± 0.03 mmol/g of kidney (uDR) corresponding to a decrease of 41.84 %. Treatment of diabetic rats with LiMAE and LiMAE-Mg significantly increased at $p < 0.05$ the activities of GSH and SOD compared to those of untreated diabetic rats. At the dose of 400 mg/kg, LiMAE-Mg significantly increased the activities of GSH and SOD respectively by 120.77% and 50.67% compared to untreated diabetic rats. At a dose of 600 mg/kg, the LiMAE and LiMAE-Mg extracts significantly increased the activity of SOD by 152.73 % and 180.90 % respectively. As for the level of GSH, it was also significantly increased at $p < 0.0001$. Respective increases of 55.20 % and 75.11% were measured for the level of GSH. The effect of Glucophage (10 mg/kg) was not significant ($p > 0.05$) on the level of GSH and SOD activity compared to untreated diabetic rats.

DISCUSSION

Administration of STZ to rats induced an elevation of lipid peroxidation (MDA) activity. Elevated MDA levels in diabetic animals are an indicator of increased reactive oxygen species production following STZ intoxication [14]. The increased elevation of free fatty acids promotes the synthesis of ceramides which will activate NO synthetase. And the excess of NO formed accentuates the formation of the nitric oxide radical, which will inhibit cytochrome C oxidase, leading to the opening of the Permeability Transition Pore (PTP) of the inner mitochondrial membrane. This breach of the PTP leads to the escape of protons and in turn leads to mitochondrial swelling, the release of cytochrome C into the cytosol and the activation of caspases, a phenomenon linked to the death of β cells [15]. Treatment of sick rats with LiMAE decreased MDA levels. This implies that the extract would have led to an inhibition of lipid peroxidation and the production of free radicals, hence the drop in MDA levels observed. This result is consistent with the work of Djoupo [16] on the antidiabetic activity of the ethanolic fraction of *Trichilia emetica*, which showed a good ability to regenerate pancreatic β cells.

SOD is able to remove the superoxide anion through a dismutation reaction. Its role is to convert superoxide radicals into hydrogen peroxide in the mitochondria [17]. These hydrogen peroxides are then reduced by catalase [18]. In addition, in the liver, heart and kidney, an increase in catalase (CAT) activity is also noted, which implies a compensatory response to oxidative stress due to the endogenous production of hydrogen peroxide. CAT is also responsible for removing hydrogen peroxide through transformation into water and oxygen. Unlike GSH, the affinity of CAT for hydrogen peroxide is high only when hydrogen peroxide levels are increased [19]. In general, the results obtained showed an increase in oxidative stress in diabetic rats compared to healthy rats. This observation suggested that the antioxidant defenses of β cells in diabetic rats are weaker than those of β cells in healthy rats. Treatment of diabetic rats with LiMAE extract revealed that the activities of oxidative stress marker enzymes (SOD, CAT and GSH) increased significantly. These results also showed the antioxidant property of LiMAE.

These results also showed that LiMAE has the ability to scavenge free radicals. Therefore, this plant extract could be used to treat many diseases caused by reactive oxygen species. These pathologies include inflammation, cancer, atherosclerosis, diabetes, among others. The action of scavenging free radicals which has been demonstrated by several studies would be attributable to the compounds contained in the antidiabetic substances [20, 21]. And at the level of medicinal plants in general and *Lippia multiflora* in particular, this action would be due to secondary metabolites and in particular polyphenols, flavonoids and tannins. These secondary metabolites, highlighted by various studies, are responsible for the antioxidant properties and consequently the antidiabetic action on oxidative stress of LiMAE [22, 23].

The results showed that the aqueous extract of *Lippia multiflora* supplemented with magnesium (LiMAE-Mg) has greater antidiabetic effects on markers of oxidative stress in STZ-diabetic rats compared to the aqueous extract (LiMAE). Magnesium would reinforce the effects of LiMAE at the level of the radical profile. The addition of magnesium would allow a greater reduction in free radicals and better fight against the effects of oxidative stress in STZ-diabetic rats. The beneficial effect of LiMAE supplementation with magnesium has already been reported by Allo *et al.*, [5]. These authors showed that LiMAE-Mg allowed, in comparison with LiMAE, a greater restoration of glycaemia, lipid profile, carbohydrate profile, cardiovascular parameters disturbed by the induction of diabetes by administration of STZ in Wistar rats. The biological parameters studied had been strongly restored with values very close and statistically identical to those of healthy animals as observed in the present study. The results obtained in the present study are also in agreement with those of many other previous works having shown beneficial effects of the supplementation of antidiabetic substances with magnesium [24-28]. These works have revealed that magnesium enhances the nephroprotective, hepatoprotective, cardioprotective, antioxidant, hypoglycemic and many other properties of antidiabetic substances.

CONCLUSION

To summarize this study, the aqueous extract of the leaves of *Lippia multiflora* (Verbenaceae) restored the activities and levels of oxidative stress markers that had been disrupted in diabetic rats. This

would militate in favor of the traditional use of this plant in the treatment of diabetes. The addition of magnesium enhanced the antidiabetic action of *Lippia multiflora* extract. Therefore, the supplementation of *Lippia multiflora* extract with magnesium could be an alternative for the development of products to treat diabetes and various diseases involving free radicals.

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AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

DECLARATIONS

The authors confirm this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

Competing Interests: The authors declare that there is no conflict of interest.

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