



## Antidiabetic Activity of Aqueous and Ethanolic Extracts of Stem Barks from *Trichilia emetica* (Meliaceae) in Alloxan-Induced Diabeticalbinos Rats

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### Authors' contributions

This work was carried out in collaboration among all authors. Authors DAP and YHF designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors DKAL, DAP and MK managed the analyses of the study. Authors DAP and TGG managed the literature searches. All authors read and approved the final manuscript.

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### ABSTRACT

**Aims:** This study was designed to evaluate the antidiabetic effects of aqueous and ethanolic extracts of *Trichilia emetica* (TE) stem bark in albinos rats.

**Methodology:** 24 rats of comparable weight were divided into 2 lots, including a control lot of 3 rats and a test lot of 21 rats. Diabetes was induced by injecting Alloxan® intraperitoneally (125 mg/kg bw) for 7 days. After the onset of diabetes, the animals were divided into several groups and given the extracts of *Trichilia emetica* and Diastabol® orally for 6 days according to the following protocol: Normal Control (NC) received normal saline, group diabetic control (DC) it consists of untreated diabetic, group DD10 and DD20 was comprised of diabetic animals treated with Diastabol® at a doses of 10 and 20 mg/kg bw respectively, group DTEE100 and DTEE200 it consists of diabetic animals treated with ethanolic extract at a doses of 100 and 200 mg/kg bw respectively, group

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DTEA100 and DDTEA 200 was comprised of diabetic animals treated with aqueous extract at a same dose (100 and 200 mg/kg bw). At the end of experimentation, some blood was collected for the determination of some biochemical parameters such as insulin, blood glucose, AST, ALT, urea and creatinine. Systolic blood pressure (SBP), diastolic blood pressure (DBP), cardiac frequency (CF) were also recorded.

**Results:** The results showed a significant ( $P < 0.05$ ) decrease in insulin levels in diabetic rats compared with NC. In addition, diabetes caused a significant increase ( $P < 0.05$ ) in blood glucose, urea, creatinine levels, transaminase activity, and in blood pressure numbers (DBP, SBP and CF) still in comparison with NC. However, the treatment of sick animals with the extracts and the Diastabol at the doses listed above significantly ( $P < 0.05$ ) increased insulin levels and reduced the same biochemical parameters levels as well as the blood pressure numbers compared with DC.

**Conclusion:** The data obtained showed that this part of the plant would have antidiabetic effects with ethanolic extract at the dose of 200 mg/kg bw had the highest pronounced effect and could be used as a good alternative for diabetes management, thus justifying its use in traditional medicine.

**Keywords:** Antidiabetic; *Trichilia emetica*; alloxan; diabetes.

## 1. INTRODUCTION

Diabetes is a ubiquitous endocrine disease characterized by high blood sugar and resulting from an absolute or relative insufficiency of insulin secretion, insulin action, or both. And chronic high blood sugar levels in diabetes are associated with long-term damage leading to dysfunction of various organs, particularly the eyes, kidneys, nerves, heart and blood vessels [1]. Therapeutic options for this condition consist of a multifactorial intervention such as regular physical activity to control heart disease and high blood pressure. There is also blood glucose control that can be achieved by oral hypoglycemic agents as well as therapeutic approaches to delay glucose absorption by inhibiting carbohydrate enzymes such as amylase and hydrolyzed glucosidases and insulin therapy [2]. However, modern medicines are very often limited due to certain side effects that affect patients' health. Thus, the introduction of alternative and complementary medicine is now on the agenda. There is therefore an increasing need to develop new diabetes prevention strategies with fewer side effects, such as phytotherapy [3]. Over the years, the use of plants in traditional medicine to treat various diseases has become popular and widely accepted throughout the world. The World Health Organization (WHO) estimates that about 80% of the population in developing countries depend mainly on this traditional medicine, which involves the use of plant extracts [4]. This is because plants generally contain a variety of chemical compounds with important biological functions. Many researchers have demonstrated that natural products are a potential source of

new drug candidates for many diseases in general and diabetes in particular. Indeed, studies have demonstrated and confirmed the hypoglycemic activity of several plants [5].

*Trichilia emetica* is a plant widely used in several traditional medicines to cure various diseases. Several pharmacological properties of this plant have been demonstrated by a number of authors. Thus, immunomodular and cardioprotective activities were investigated to name a few [6,7]. Diabetes-related studies have mostly been carried out on extracts from the leaves of this plant but not on stem bark extracts. However, the phytochemical study of aqueous and ethanolic extracts of this part of the plant revealed the presence of several groups of secondary metabolites [6]. Therefore, this study was conducted to evaluate the antidiabetic potential of ethanolic and aqueous extracts from stem bark of *Trichilia emetica* in alloxan-induced diabetic.

## 2. MATERIALS AND METHODS

### 2.1 Materials

The plant material was made up of the *Trichilia emetica* (Meliaceae) stem barks from the African pharmacopoeia. The plant was identified at the National Center of the Floristry of the Félix Houphouët Boigny University in Abidjan, Cocody. The collection of fresh stem barks was done during ethnopharmacological investigations in February 2014 in the North of Côte d'Ivoire.

Albinos Wistar healthy rats obtained from an Animal House are used for this study. The

animals were kept in plastic cages in the environmental conditions. They had free access to standard food pellets and were allowed to drink water *ad libitum*. Animal care and handling conformed to international guidelines (european council legislation 87/607/eec).

## 2.2 Methods

### 2.2.1 Preparation of the extract

The extracts were prepared according to the method described by Zirihi et al. [8]. The preparation of the total aqueous extract and ethanolic extract 70%, 100 g of plant powder were extracted in one liter of distilled water or ethanol-water (70/30, v/v) by maceration using a magnetic agitator (the process was repeated 3 times). The homogenate obtained is filtered twice successively on cotton wool and once on Whatman filter paper (3 mm). The filtrate was concentrated using a rotary evaporator at 60°C. The concentrate have been evaporated at 50°C in an oven for 48 hours giving a dry ethanolic and aqueous extract. The powder obtained after drying was dissolved in distilled water to give the aqueous and ethanolic extracts of bark from *Trichilia emetica*. Thus, different concentrations were prepared to carry out the experiments.

### 2.2.2 Experimental design

Diabetes induction was performed using the method of Diatewa et al. [9]. A total of 24 rats of comparable weight were divided into 2 lots, including a control lot of 3 rats and a test lot of 21 rats. Diabetes was induced by injecting Alloxan® intraperitoneally (125 mg/kg bw) in solution in 0.1 M pH 4.5 citrate buffer for 7 days.

After the onset of diabetes, the animals were divided into several groups and given the extracts of *Trichilia emetica* and Diastabol® (reference antidiabetic drug) orally for 6 days according to the following protocol: Normal Control (NC) received normal saline, diabetic control (DC) it consists of untreated diabetic and was used as a control for the batches made diabetic and treated, DD10 and DD20 was comprised of diabetic animals treated with Diastabol® at a doses of 10 and 20 mg/kg bw respectively, DTEE100 and DTEE200 it consists of diabetic animals treated with ethanolic extract

at a doses of 100 and 200 mg/kg bw respectively, DTEA100 and DTEA 200 was comprised of diabetic animals treated with aqueous extract at a same dose (100 and 200 mg/kg bw). At the end of experimentation, some blood was collected for the determination of some biochemical parameters such as insulin, blood glucose, AST, ALT, urea and creatinine. Systolic blood pressure (SBP), diastolic blood pressure (DBP), cardiac frequency (CF) were also recorded.

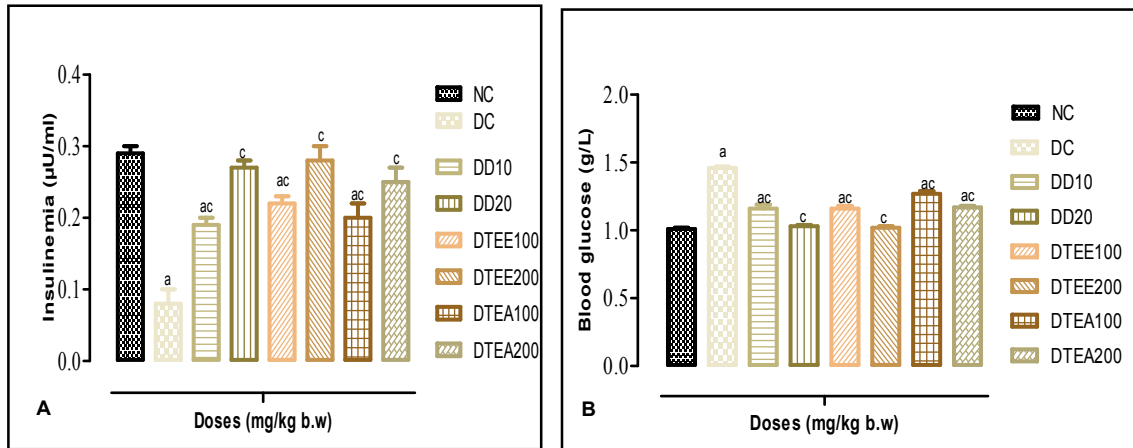
## 2.3 Statistical Analysis

The analysis of the results used the Tukey's test, which was performed with Graph Pad Prism software 5.0 (Microsoft, USA). The average value is accompanied by the standard error of the mean (mean  $\pm$  SEM). The difference between the two values is considered significant when  $P < 0.05$ . The Statistical analysis of these results was performed using an analysis of variance (ANOVA).

## 3. RESULTS

### 3.1 Effects of *Trichilia emetica* (Meliaceae) Extracts and Diastabol® on Insulin Levels in rats with Diabetes

The results showed that, administration of Alloxan to rats resulted in a significant decrease ( $P < 0.05$ ) in insulin levels from  $0.29 \pm 0.01$   $\mu\text{U/mL}$  in controls to  $0.08 \pm 0.0201$   $\mu\text{U/mL}$  in diabetic rats, a percentage reduction of 72.41%. After treatment of diabetic rats with *Trichilia emetica* extracts and Diastabol® the reference anti-diabetic molecule, insulin levels increased significantly ( $P < 0.05$ ) compared to untreated diabetic rats. The insulinemia values recorded with ethanol extract at doses of 100 mg/kg bw and 200 mg/kg bw are  $0.22 \pm 0.01$   $\mu\text{U/mL}$  and  $0.28 \pm 0.02$   $\mu\text{U/mL}$ , i.e. percentages increase of 175.00% and 250.00% respectively. Aqueousextract at 100 and 200 mg/kg bw elevated the blood insulin level by  $0.19 \pm 0.01$   $\mu\text{U/mL}$  and  $0.22 \pm 0.01$   $\mu\text{U/mL}$ , a percentage increase of 150.00% and 212.50% respectively compared to untreated diabetic rats. Diastabol® at 10 mg/kg bw increased insulin levels by 137.50% and 20 mg/kg bw by 237.50% compared to untreated diabetic rats (Fig. 1A).



**Fig. 1. Effect of *Trichilia emetica* extracts and Diastabol® on serum insulin (A) and blood glucose (B) concentration in rats made diabetic**

Each bar represents the mean  $\pm$  SEM=Mean values  $\pm$  Standard error of means of 3 experiments (n=3); a = \*\*\*  $P < 0.001$  = significant difference when compared to NC ; b= \* $P < 0.05$  = significant difference when compared to NC, c= \*\*\* $P < 0.001$  = significant difference when compared to DC

### 3.2 Effects of *Trichilia emetica* (Meliaceae) Extracts and Diastabol® on Blood Glucose Levels in rats with Diabetes

Diabetes induced in rats by Alloxan injection resulted in a significant increase ( $P < 0.05$ ) in blood glucose levels in diabetic animals to  $1.46 \pm 0.01$  g/L compared to  $1.01 \pm 0.01$  g/L in control rats, an increase of 44.55%. The treatment of diabetic animals with *Trichilia emetica* extracts and Diastabol® has resulted in a significant decrease ( $P < 0.05$ ) in blood sugar levels. Aqueous extract at 100 and 200 mg/kg bw resulted in a 13.01% and 19.86% decrease in blood glucose levels compared to untreated diabetic rats, respectively. Ethanolic extract at the same doses reduced blood glucose levels by 20.55% and 30.13% respectively compared to the untreated diabetic lot. Diastabol® also decreased blood glucose levels by 20.55% at 10 mg/kg bw and 29.45% at 20 mg/kg (Fig. 1B).

### 3.3 Effects of *Trichilia emetica* (Meliaceae) Extrats and Diastabol® on Transaminases Activity, Creatinine and Urea Levels in rats with Diabetes

Transaminases activity, serum creatinine and urea levels were increased significantly ( $P < 0.05$ ) with alloxan induced diabetes respectively of 140% approximately and 44.92% (AST), (ALT) 58.87%. Treatment of animals with 100 and 200 mg/kg bw of aqueous and ethanolic extracts of *Trichilia emetica* and Diastabol (10 and 20 mg/kg bw)

induced significant decrease in the level of serum of this biochemical parameters compared to the untreated diabetic lot (Fig. 2C, 2D & Fig. 3).

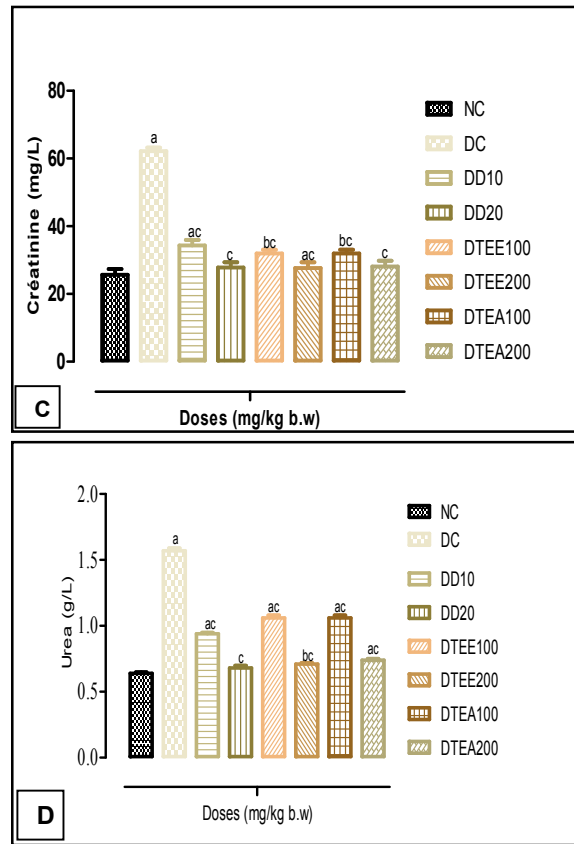
### 3.4 Effects of *Trichilia emetica* (Meliaceae) Extrats and Diastabol® on Cardiovascular Parameters Levels in rats with Diabetes

Fig. 4 shows that systolic blood pressure increased significantly ( $P < 0.05$ ) to  $169 \pm 1.00$  mmHg in diabetic rats compared to  $124.2 \pm 2.14$  mmHg in control rats, a percentage increase of 36.07%. In these same diseased rats, diastolic blood pressure also increased to  $142.1 \pm 1.57$  mmHg from  $100.4 \pm 1.45$  mmHg in controls, an increase of 41.53%. Cardiac frequency also increased in diabetic rats to  $266 \pm 2.08$  beats/min from  $226.7 \pm 1.33$  beats/min in controls, an increase of 17.34%. However, the administration of extracts at doses of 100 and 200 mg/kg bw significantly decreased these same blood pressure figures. The same applies to Diastabol® at doses of 10 and 20 mg/kg bw.

## 4. DISCUSSION AND CONCLUSION

### 4.1 Discussion

Alloxan is a cytotoxin used to induce type 1 diabetes in a wide variety of animal species. Indeed, within 24 to 48 hours after its administration, Alloxan selectively induces pancreatic necrosis of the cells  $\beta$  of the islets of Langerhans by complete degranulation and the

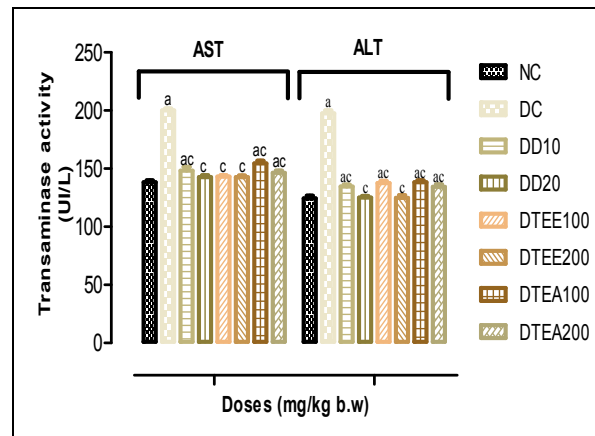


**Fig. 2. Effects of *Trichilia emetica* (Meliaceae) extracts and Diastabol® on creatinine (C) and urea (D) levels in rats with diabetes**

Each bar represents the mean  $\pm$  SEM=Mean values  $\pm$  Standard error of 3 experiments (n=3); a = \*\*\* P< 0.001) = significant difference when compared to NC ; b= \*P< 0.05 = significant difference when compared to NC, c= \*\*\*P< 0.001 = significant difference when compared to DC

loss of their integrity [10]. This has the consequence of a massive reduction in insulin release, which leads to a state of hyperglycemia as observed in our study in diabetic animals. However, treatment of diabetic rats with aqueous and ethanolic extracts of *Trichilia emetica* at doses of 100 mg/kg bw and 200 mg/kg bw and Diastabol® (10 mg/kg bw and 20 mg/kg bw) resulted in a significant decrease in blood glucose levels and a significant increase in insulin levels. The same effect has been shown by other authors with the treatment of diabetic rats with plants extracts [11]. The increase in insulin levels by the extracts shows that the extracts would have acted, either by regenerating pancreatic cells destroyed by alloxan or by simulating the rapid effect of insulin. Another possibility is that they may have had a residual effect by promoting better use of insulin by target cells and organs [12]

The decrease in blood glucose levels induced by the extracts could be explained by the fact that the extracts acted like Diastabol®, which is an inhibitor of  $\alpha$ -glucosidase. Indeed, intestinal  $\alpha$ -glucosidases are enzymes that are found on the surface of the villi in the small intestine. They are responsible for hydrolyzing starch residues, oligosaccharides and disaccharides to release glucose. This hydrolysis is necessary for the digestive absorption of carbohydrates, since only monosaccharides (glucose or fructose) can be absorbed. Inhibition of this enzyme reduces or slows down the intestinal digestive absorption of glucose, thus leading to a decrease in postprandial glucose levels. This decrease in blood glucose levels from extracts may also be due to the fact that extracts have the potential to increase glucose utilization by peripheral tissues (muscle and fat tissue) or decrease glucose production by the liver [13].



**Fig. 3. Effects of *Trichilia emetica* (Meliaceae) extracts and Diastabol® on transaminase level in rats with diabetes**

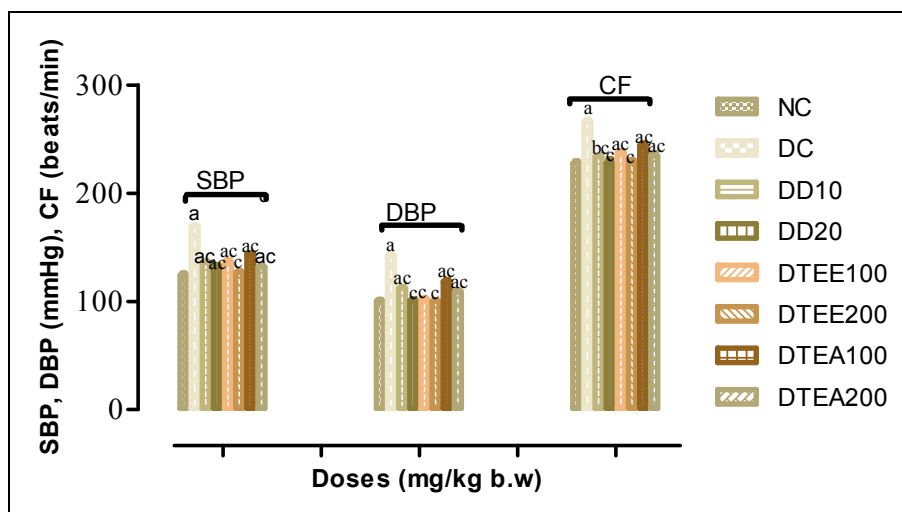
Each bar represents the mean  $\pm$  SEM=Mean values  $\pm$  Standard error of means of 3 experiments ( $n=3$ );  $a = ***P < 0.001$ ) = significant difference when compared to NC ;  $b = *P < 0.05$  = significant difference when compared to NC,  $c = ***P < 0.001$  = significant difference when compared to DC

Diabetes has also caused elevated of liver transaminases activity such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in animals with diabetes. In general, the elevation of transaminases activity in the blood, especially ALT, is an indicator of damage to parachute cells in the liver [14]. This would mean that diabetes has caused liver damage, resulting in increased transaminases in sick rats. The treatment of sick animals with extracts significantly decreased serum transaminase levels. This suggests that the extracts could protect the liver from the harmful effects of diabetes.

It is well known that diabetic nephropathy is one of the complications caused during the progression of diabetes. It is characterized by tubule necrosis, glomerulus atrophy, and capillary congestions. This results in a decrease in the renal elimination of some metabolic waste products such as creatinine and urea. Creatinine and urea are nitrogenous end products of metabolism that reflect the glomerular filtration rate. Creatinine is produced after the cleavage of phosphocreatine pyrophosphate to produce energy for muscle activity [15]. As for urea, it is produced from the oxidative deamination of amino acids in which the ammonia produced is transported to the liver to be transformed into urea by the urea cycle. It is clear that an increase in blood levels of these two biochemical parameters indicates a deficit in kidney excretion function. In this study, the higher creatinine and urea levels in diabetic rats compared to control

rats is an indication of renal dysfunction and metabolic disorders induced by diabetes [16]. The administration of extracts to diabetic rats significantly reduced serum levels of these kidney markers, indicating that aqueous and ethanolic extracts of *Trichilia emetica* steem bark would protect the kidneys from disturbances due to this complication of diabetes in its evolution. In addition, vascular damage caused by chronic hyperglycemia in diabetes accelerates the progression of cardiovascular diseases (CVD) such as high blood pressure. Thus, hypertension reaches 50 to 75% of diabetics with a different mechanism depending on the type of diabetes [17]. In type 1, it is essentially secondary to kidney disease, while in type 2, it is linked to insulin resistance and often precedes the development of hyperglycemia [18]. The significant increase in Systolic blood pressure (SBP), diastolic blood pressure (DBP) and cardiac frequency in diabeticanimals observed in this experiment is a secondary hypertension due to the diabetic nephropathy observed. The decrease in blood pressure after administration of *Trichilia emetica* extracts to sick animals suggests that they may contain bioactive substances that may be beneficial for the treatment of hypertension.

The significant decrease in serum levels of liver, kidney and blood pressure parameters, blood glucose and the restoration of insulin levels, particularly with ethanolic extract at a dose of 200 mg/kg/bw, may be an indication that this concentration is the best and safest to use when



**Fig. 4. Effects of *Trichilia emetica* (Meliaceae) extracts and Diastabol® on cardiovascular parameters in rats with diabetes**

Each bar represents the mean  $\pm$  SEM=Mean values  $\pm$  Standard error of means of 3 experiments ( $n=3$ ); a = \*\*\*  $P < 0.001$  = significant difference when compared to NC ; b= \* $P < 0.05$  = significant difference when compared to NC, c= \*\*\* $P < 0.001$  = significant difference when compared to DC

administering this extract. Therefore, it could be used as a good alternative in the management of diabetes.

## 4.2 Conclusion

The antidiabetic activity of ethanolic and aqueous extracts of *Trichilia emetica* stem bark was investigated. The results obtained showed that the extracts have the potential to reduce high blood glucose and increase insulin levels in rats with alloxan-induced diabetes. In addition, they had a protective effect on the liver, kidney and cardiac functions in these same diseased animals. These results suggest that these are potential antidiabetic extracts that may lead to the discovery of new drugs. However, further studies are needed to investigate the antidiabetic compounds present that could justify these activities and also in the design of therapeutic alternatives for the treatment of diabetes; especially with ethanolic extract at the higher dose that showed more pronounced activity.

## ETHICAL APPROVAL

The experimental procedures and protocols used in this study were approved by the ethical committee in accordance with the European Council legislation 87/607/EEC for the protection of experimental animals. All efforts were made to

minimize animal suffering and reduce the number of animals used.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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