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# Influence of lauric acid on the relaxation of corpus cavernosum in streptozotocin-induced diabetic male Wistar rats

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## Abstract

**Background:** Diabetes mellitus is a global health challenge and has been recognised as a risk factor for erectile dysfunction. Dissatisfaction with standard medications has been reported by some patients, hence therapeutic plants are being considered as a viable alternative therapy, with their active components being investigated to create a standard regimen. Lauric acid is the most abundant constituent of coconut oil and is proposed to be responsible for its therapeutic properties. The corpus cavernosum plays an important role in erectile function with its relaxation favouring erection. This study thus sought to investigate the possible relaxant action and mechanism of lauric acid on the corpus cavernosum of diabetic male Wistar rats. Diabetes was induced by intraperitoneal injection of streptozotocin after which graded doses of lauric acid were administered orally to three groups of diabetic rats, once daily for 4 weeks. At the end of the experiment, the corpus cavernosal tissues of the rat penis were extracted. Following phenylephrine or potassium chloride (KCl)—induced contraction, relaxation response to acetylcholine and sodium nitroprusside was used to evaluate endothelium-dependent and nitric oxide-mediated relaxation, respectively.

**Results:** Relaxation response to acetylcholine, following pre-contraction with phenylephrine, was significantly decreased in the cavernosal tissues of diabetic untreated rats and was not significantly improved in lauric acid treated diabetic groups. Relaxation response to acetylcholine, following pre-contraction with KCl, was significantly decreased in the diabetic untreated group but was significantly improved in lauric acid treated diabetic groups at the lowest dose. Decreased relaxation response to sodium nitroprusside, following pre-contraction with phenylephrine in tissues of diabetic untreated rats, was significantly improved in lauric acid-treated diabetic groups at lower doses. Decreased relaxation response to sodium nitroprusside, following pre-contraction with KCl, was significantly improved in lauric acid-treated diabetic groups at all doses.

**Conclusion:** Lauric acid improved relaxation of corpus cavernosum muscle in diabetic male rats by enhancing nitric oxide-mediated relaxing action of sodium nitroprusside and possibly inhibiting KCl-induced contraction.

**Keywords:** Lauric acid, Diabetes mellitus, Corpus cavernosum, Smooth muscle contraction

## Background

Diabetes mellitus is a metabolic syndrome characterised by chronic hyperglycaemia due to deficient insulin production by the pancreas, inefficient insulin action or both. It is a global health challenge affecting about 422

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million adults worldwide and is estimated to double by 2025 with greater threats to developing countries [1]. It is associated with some complications across the body systems, e.g. retinopathy, neuropathy, nephropathy, cardiovascular, reproductive dysfunction, etc. [2].

Erectile dysfunction (ED) is the continual incapacity to achieve and/or maintain a sufficient erection necessary to complete a satisfactory sexual activity [3]. Its global prevalence was projected at 322 million by 2025, which is almost double that reported in 1995 [4]. Diabetes mellitus has been identified as a risk factor for erectile dysfunction [1]. Erectile dysfunction has been reported to be more prevalent among diabetic patients than in the general population [5].

Erection is triggered by tactile or psychic sexual stimulation, which causes impulses to be sent through the parasympathetic nervous system, and the nitrergic nerves (non-adrenergic non-cholinergic nerve fibres). The parasympathetic nerve fibres release acetylcholine which acts on the endothelium of the corpus cavernosum and penile vessels to release nitric oxide (NO). The nitrergic nerves directly release NO [6]. The NO causes an increase in the production of cyclic guanosine monophosphate (cGMP) which stimulates a cascade of other processes that eventually lead to the relaxation of the smooth muscles of the corpus cavernosum, increased dilation of the penile arteries and increased blood flow. The increased blood flow coupled with venous occlusion cause filling of the cavernosal sinuses thus leading to an erection. Erection is terminated by the reduction in the parasympathetic impulses and release of norepinephrine by the sympathetic nerves, thus causing contraction of the corpus cavernosum and consequently detumescence [7].

Sildenafil, a phosphodiesterase 5 (PDE5) inhibitor, is a commonly prescribed standard drug for erectile dysfunction. It prevents the metabolism of cGMP which mediates the relaxant action of NO in the erectile tissues. The consequently increased bioavailability of cGMP by sildenafil thus favours and sustains erection [8]. However, there have been reports of discontentment by some patients with sildenafil. This is due to the cost and adverse effects among other shortcomings [9]. In addition, some diabetic patients with erectile dysfunction do not respond favourably or exhibit resistance to sildenafil [10].

Medicinal plants have been used as therapy for various ailments. They offer a cheaper, affordable and more readily available alternative therapy. However, their active components and mechanisms of action need to be investigated to create a standard therapeutic product [11].

Lauric acid is a medium chain saturated fatty acid. It is the most abundant constituent of coconut oil, making up about 50% of the total composition. Thus, lauric acid is hypothesised to contribute greatly to the physiologic

effects of coconut oil [12]. Coconut oil is largely consumed in the tropics and is renowned for its nutritional and medicinal value. Research has proven it possesses anti-diabetic properties [13] and ameliorative effects on reproductive dysfunction [14]. Lauric acid has been specifically reported to possess vaso-relaxant effects [15]. However, there is a dearth of scientific information about the effects of lauric acid on erectile dysfunction with emphasis on the relaxation of corpus cavernosum smooth muscle in diabetic conditions.

The aim of this study was to investigate the relaxant effects of lauric acid on the corpus cavernosum smooth muscle of diabetic male Wistar rats.

## Methods

### Chemicals/drugs

Lauric acid, Sodium nitroprusside (SNP), Acetylcholine (Ach), Phenylephrine (PE) and Streptozocin were obtained from Ak Scientific Inc. (USA) Sildenafil citrate was obtained from Pfizer pharmaceutical company (USA).

### Animals

Thirty male Wistar rats (12 weeks old) weighing 150–200 g were used. The animals were kept in the animal house of Human Physiology Department, Ahmadu Bello University (ABU), Zaria. They were maintained under standard conditions and given food and water ad libitum. Ethical approval was obtained from the Ahmadu Bello University Animal care and use committee with the approval number, ABUCAUC/2017/019. Animals were handled in compliance with the World Medical Association Declaration of Helsinki regarding the ethical conduct of research involving animals [16].

The animals were divided into six groups ( $n=5$ ) as follows:

*Group 1 (NC)* Normal Control animals

*Group 2 (DM-UT)* Diabetic untreated animals

*Group 3 (DM + LA 90)* Diabetic treated with lauric acid 90 mg/Kg orally

*Group 4 (DM + LA 180)* Diabetic treated with lauric acid 180 mg/Kg orally [17]

*Group 5 (DM + LA 360)* Diabetic treated with lauric acid 360 mg/Kg orally [17]

*Group 6 (DM + Sild)* Diabetic rats treated with Sildenafil (20 mg/Kg) [18]

Diabetes was induced with diabetes by the administration of a single intraperitoneal injection of streptozotocin (65 mg/kg) in 0.1 M citric acid buffer at pH 4.5 [19]. The blood glucose level of the rats was checked 3 days after. Animals with fasting blood glucose levels greater than

200 mg/dL were marked as diabetic and placed in the diabetic groups (groups 2, 3 and 4 and 5). All treatments were for 4 weeks, and then the animals were sacrificed by cervical dislocation following chloroform inhalation.

#### Acute toxicity study

The acute toxicity was estimated following Lorke's method [20], which involves two phases. For the first phase, nine male Wistar rats were divided into three groups of three rats each. Each group received 10, 100 and 1000 mg/kg of lauric acid, respectively. For the second phase, three male Wistar rats were divided into three groups of one rat each. Each group received 1600, 2900 and 5000 mg/kg of lauric acid, respectively. In both phases, the animals were observed for 24 h for any case of mortality or abnormal behaviour [21].

#### Measurement of blood glucose level

Blood glucose level was measured with the aid of the Accu-Chek glucose glucometer (Roche, USA), which works based on the glucose oxidase principle [22]. Blood was obtained by pricking the tip of the rat tail with a lancet.

#### Tissue preparation

After the rat has been sacrificed, the penis was cut out as a whole. The corpus cavernosum was then isolated from the surrounding penile tissues. Each cavernosal strip with both ends tied with a silk thread was placed in a 50 mL organ bath chamber filled with Krebs buffer solution with the following composition NaCl (119 mM), KCl (4.7 mM),  $\text{NaHCO}_3$  (15 mM),  $\text{KH}_2\text{PO}_4$  (1.2 mM),  $\text{MgSO}_4$  (1.2 mM),  $\text{CaCl}_2$  (1.6 mM), and Glucose (11.5 mM). The Krebs solution was supplied with 95%  $\text{O}_2$  and 5%  $\text{CO}_2$  and maintained at a temperature of 37 °C. One end of the cavernosal strip was tied to a tissue holder and the other knotted to an Ugo Basile 7004 force transducer (Ugo Basile, Varese, Italy). The force transducer was connected to a 17,400 data capsule (Ugo Basile, Varese, Italy) which was then connected to a computer system. Thus, data relating to the contraction and relaxation response of the cavernosal tissues could be captured, displayed and then analysed. 2 g of tension was applied to each strip and allowed to equilibrate for 60–90 min. During the equilibration periods, the tissue was contracted with phenylephrine once every 30 min, and the organ bath solution was washed off and replaced 5 min after each injection of phenylephrine. Thereafter the contractile or relaxant responses of the tissue to the test drugs were evaluated [23].

#### Relaxation response to acetylcholine

Relaxation response of the corpus cavernosal strip to acetylcholine was used to evaluate endothelium-dependent relaxation. Following a contraction of the cavernosal strip with phenylephrine ( $10^{-7}$ ) or KCl (60 mM), the cumulative concentration of ( $10^{-9}$ – $10^{-3}$  M) was added to the organ bath. The concentration-relaxation response was then obtained [24]

#### Relaxation response to sodium nitroprusside

Relaxation response of the corpus cavernosal strip to sodium nitroprusside (SNP) was used to evaluate endothelium-independent relaxation. Cumulative doses of Sodium nitroprusside (SNP) ( $10^{-9}$ – $10^{-4}$  M) were injected into the organ bath after pre-contracting the tissues with phenylephrine ( $10^{-7}$ ) or KCl (60 mM) [24].

#### Statistical analysis

The contraction or relaxation responses were evaluated as percentage contraction or relaxation. The final results were presented as mean  $\pm$  standard deviation (SD). Data were analysed using ANOVA and Bonferroni post-tests with the aid of *Graph pad prism* 5. Values with  $P < 0.05$  were considered significant.

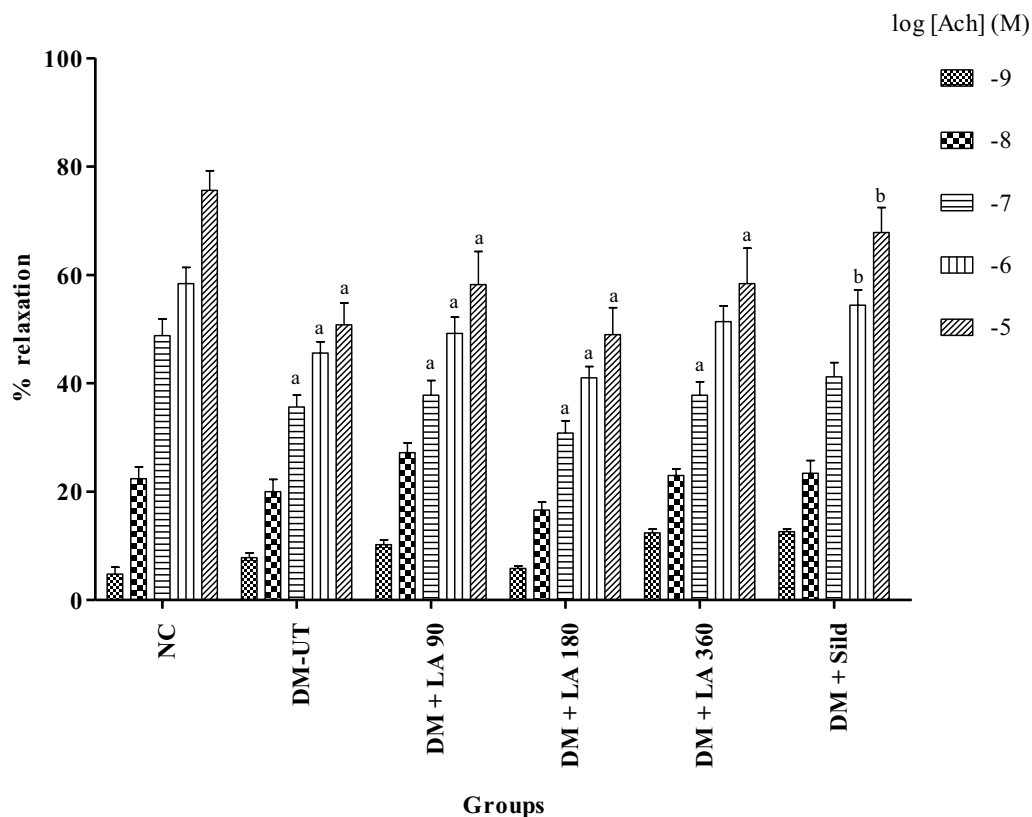
### Results

#### Acute toxicity studies

No case of mortality or sign of toxicity was observed in the two phases. This indicates that the median lethal dose ( $\text{LD}_{50}$ ) is above 5000 mg/kg and the male Wistar rats are tolerant to lauric acid.

#### Relaxation response of phenylephrine pre-contracted cavernosal tissues to cumulative concentrations of acetylcholine

As shown in Fig. 1, the percentage relaxation was significantly lower ( $p < 0.05$ ) in DM-UT compared to NC at concentrations of  $10^{-7}$  M ( $35.6 \pm 4.9$  vs  $48.8 \pm 6.9$ ),  $10^{-6}$  M ( $45.6 \pm 4.6$  vs  $58.4 \pm 6.7$ ) and  $10^{-5}$  M ( $50.8 \pm 4.0$  vs  $75.6 \pm 3.6$ ); significantly lower ( $p < 0.05$ ) in DM + LA 90 compared to NC at the concentrations of  $10^{-7}$  M ( $37.8 \pm 6.0$  vs  $48.8 \pm 6.9$ ),  $10^{-6}$  M ( $49.2 \pm 6.7$  vs  $58.4 \pm 6.7$ ) and  $10^{-5}$  M ( $58.2 \pm 6.1$  vs  $75.6 \pm 3.6$ ); significantly lower ( $p < 0.05$ ) in DM + LA 180 compared to NC rats at concentrations of  $10^{-7}$  M ( $30.8 \pm 5.1$  vs  $48.8 \pm 6.9$ ),  $10^{-6}$  M ( $41.0 \pm 4.6$  vs  $58.4 \pm 6.7$ ) and  $10^{-5}$  M ( $49.0 \pm 4.9$  vs  $75.6 \pm 3.6$ ); and significantly lower ( $p < 0.05$ ) in DM + LA 360 compared to NC at concentrations of  $10^{-7}$  M ( $37.8 \pm 5.5$  vs  $48.8 \pm 6.9$ ) and  $10^{-5}$  M ( $58.4 \pm 6.5$  vs  $75.6 \pm 3.6$ ), respectively. However, compared to DM-UT, the percentage relaxation was



**Fig. 1** Relaxation response of phenylephrine pre-contracted corpus cavernosum to cumulative concentrations of acetylcholine. NC normal control, DM-UT diabetic untreated, DM + LA 90 diabetic treated with lauric acid (90 mg/kg), DM + LA 180 diabetic treated with lauric acid (180 mg/kg), DM + LA 360 diabetic treated with lauric acid (360 mg/kg), DM + Sild diabetic treated with sildenafil. (a) Significant compared to NC ( $p < 0.05$ ); (b) significant compared to DM-UT ( $p < 0.05$ )

significantly higher ( $p < 0.05$ ) in DM + Sild at the concentration of  $10^{-6}$  M ( $54.4 \pm 6.3$  vs  $45.6 \pm 4.6$ ),  $10^{-5}$  M ( $67.8 \pm 4.7$  vs  $50.8 \pm 4.0$ ).

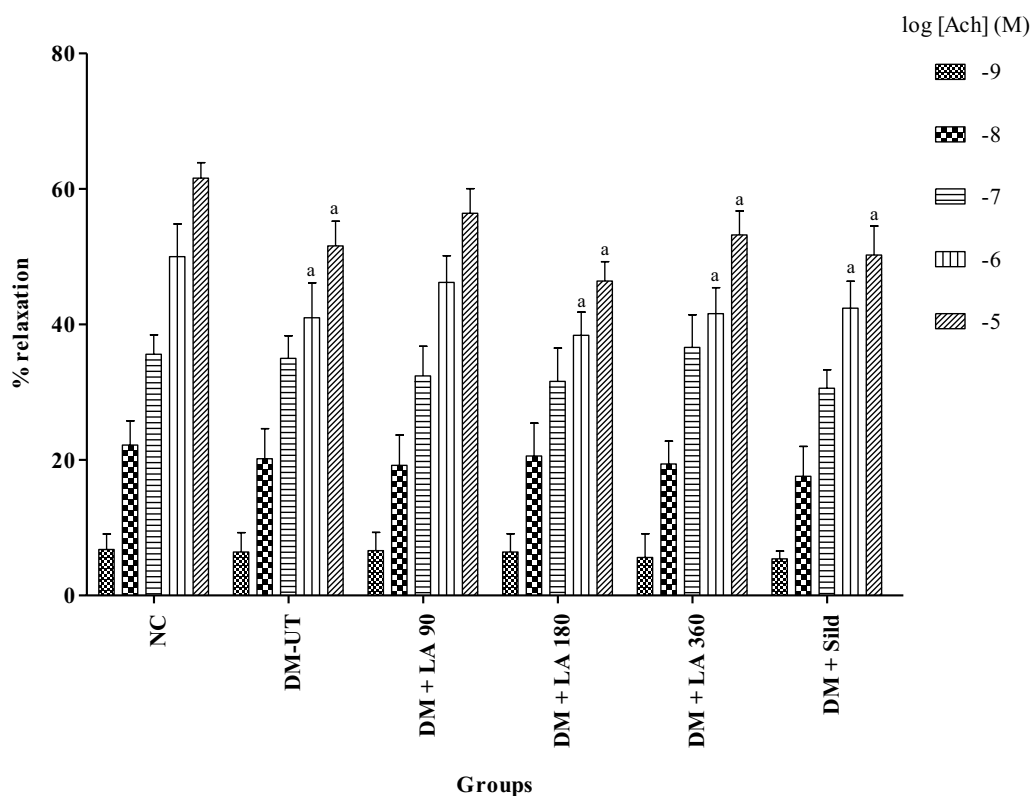
#### Relaxation response of KCl pre-contracted cavernosal tissues to cumulative concentrations of acetylcholine

As shown in Fig. 2, the percentage relaxation in DM-UT compared to NC was significantly lower ( $p < 0.05$ ) at concentrations of  $10^{-6}$  M ( $41.0 \pm 5.1$  vs  $50.0 \pm 4.8$ ) and  $10^{-5}$  M ( $51.6 \pm 3.6$  vs  $61.6 \pm 2.3$ ); lower ( $p < 0.05$ ) in DM + LA 180 compared to the NC at concentrations of  $10^{-6}$  M ( $38.4 \pm 3.4$  vs  $50.0 \pm 4.8$ ) and  $10^{-5}$  M ( $46.4 \pm 2.9$  vs  $61.6 \pm 2.3$ ); lower ( $p < 0.05$ ) in DM + LA 360 compared to the NC at concentrations of  $10^{-6}$  M ( $41.6 \pm 3.8$  vs  $50.0 \pm 4.8$ ) and  $10^{-5}$  M ( $53.2 \pm 3.6$  vs  $61.6 \pm 2.3$ ); and significantly lower ( $p < 0.05$ ) in DM + Sild compared to the NC at concentrations of  $10^{-6}$  M ( $42.4 \pm 4.0$  vs  $50.0 \pm 4.8$ ) and  $10^{-5}$  M ( $50.3 \pm 4.3$  vs  $61.6 \pm 2.3$ ), respectively.

#### Relaxation response of phenylephrine pre-contracted cavernosal tissues to cumulative concentrations of sodium nitroprusside (SNP)

As shown in Fig. 3, compared to NC, the percentage relaxation was significantly lower ( $p < 0.05$ ) in DM-UT at the concentration of  $10^{-5}$  M ( $50.0 \pm 2.5$  vs  $60.6 \pm 3.0$ ); significantly lower ( $p < 0.05$ ) in DM + LA 360 at concentrations of  $10^{-7}$  M ( $23.8 \pm 4.9$  vs  $36.0 \pm 2.9$ ),  $10^{-6}$  M ( $33.0 \pm 6.9$  vs  $47.6 \pm 6.2$ ), and  $10^{-5}$  M ( $41.2 \pm 2.9$  vs  $60.6 \pm 3.0$ ), respectively.

Similarly, compared to DM-UT, the percentage relaxation was significantly lower ( $p < 0.05$ ) in DM + LA 360 at the concentrations of  $10^{-8}$  M ( $11.2 \pm 4.0$  vs  $23.0 \pm 2.9$ ),  $10^{-7}$  M ( $23.8 \pm 4.9$  vs  $34.8 \pm 4.4$ ),  $10^{-6}$  M ( $33.0 \pm 6.9$  vs  $44.0 \pm 4.5$ ), and  $10^{-5}$  M ( $41.2 \pm 2.9$  vs  $50.0 \pm 2.5$ ), respectively; but significantly higher ( $p < 0.05$ ) in DM + Sild group at the concentrations of  $10^{-6}$  M ( $53.4 \pm 6.5$  vs  $44.0 \pm 4.5$ ) and  $10^{-5}$  M ( $67.4 \pm 4.8$  vs  $50.0 \pm 2.5$ ), respectively.



**Fig. 2** Relaxation response of KCl pre-contracted corpus cavernosum to cumulative concentrations of acetylcholine. NC normal control, DM-UT diabetic untreated, DM + LA 90 diabetic treated with lauric acid (90 mg/kg), DM + LA 180 diabetic treated with lauric acid (180 mg/kg), DM + LA 360 diabetic treated with lauric acid (360 mg/kg), DM + Sild diabetic treated with sildenafil. (a) Significant compared to NC ( $p < 0.05$ ); (b) significant compared to DM-UT ( $p < 0.05$ )

### Relaxation response of KCl pre-contracted cavernosal tissues to cumulative concentrations of SNP

As shown in Fig. 4, the percentage relaxation was significantly lower ( $p < 0.05$ ) in DM-UT rats compared to NC at the concentration of  $10^{-7}$  M ( $29.4 \pm 4.8$  vs  $41.0 \pm 6.5$ ).

Compared to DM-UT rats: the percentage relaxation was significantly higher ( $p < 0.05$ ) in DM + LA 360 rats at the concentration of  $10^{-7}$  M ( $41.2 \pm 5.3$  vs  $29.4 \pm 4.8$ ); and significantly higher ( $p < 0.05$ ) in DM + Sild rats at the concentration of  $10^{-8}$  M ( $31.0 \pm 4.5$  vs  $16.4 \pm 4.4$ ).

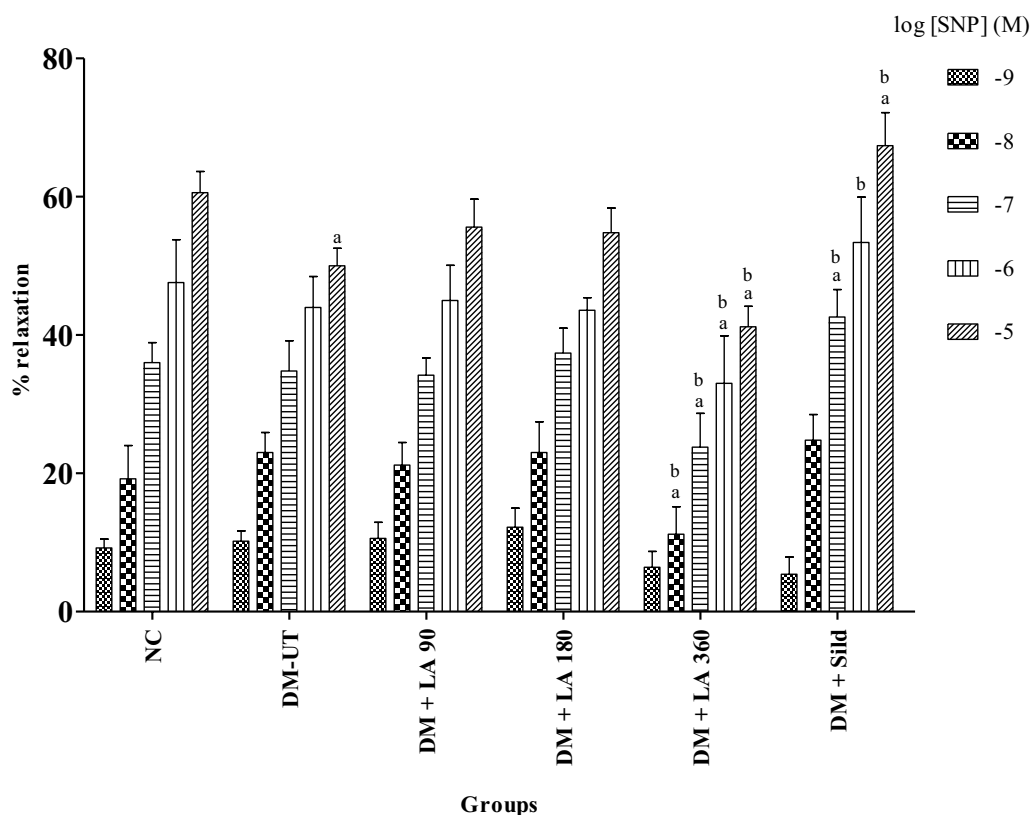
### Discussion

In cavernosal strips pre-contracted with phenylephrine and potassium chloride (KCl), respectively, there was a decline in the relaxation response of the cavernosal tissues of the diabetic untreated rats to acetylcholine. This suggests the possibility of endothelial dysfunction, an associated complication of diabetes as reported by Sánchez et al. [25], thus compromising the potency of acetylcholine in stimulating the production of nitric oxide (NO) by the endothelium. This could be responsible for reduced relaxation as nitric oxide plays a major role in

smooth muscle relaxation. The failure of lauric acid to improve the relaxation in phenylephrine contracted tissues suggests the inability to reverse the endothelial damage or impairment in erectile response to parasympathetic stimulation. However, there was an appreciable improvement in relaxation in KCl pre-contracted tissues of diabetic rats treated with the lowest dose of lauric acid (90 mg/Kg). A high concentration of potassium ion ( $K^+$ ) has been reported to increase membrane depolarization, leading to the influx of calcium ion ( $Ca^{2+}$ ) through voltage-gated calcium channels [26]. Inhibition of this mechanism would lead to reduced contraction and may be responsible for enhancing the relaxant effect of acetylcholine in KCl contracted tissues observed in this study.

The difference in the relaxation response between phenylephrine and KCl pre-contracted tissues could be due to the differences in their forces of contraction. Contractile agents like phenylephrine, which act on G protein-coupled receptors have been shown to produce a greater force of contraction compared to KCl. This is because G proteins activate other cellular processes apart from leading to increased calcium sensitivity of the contractile





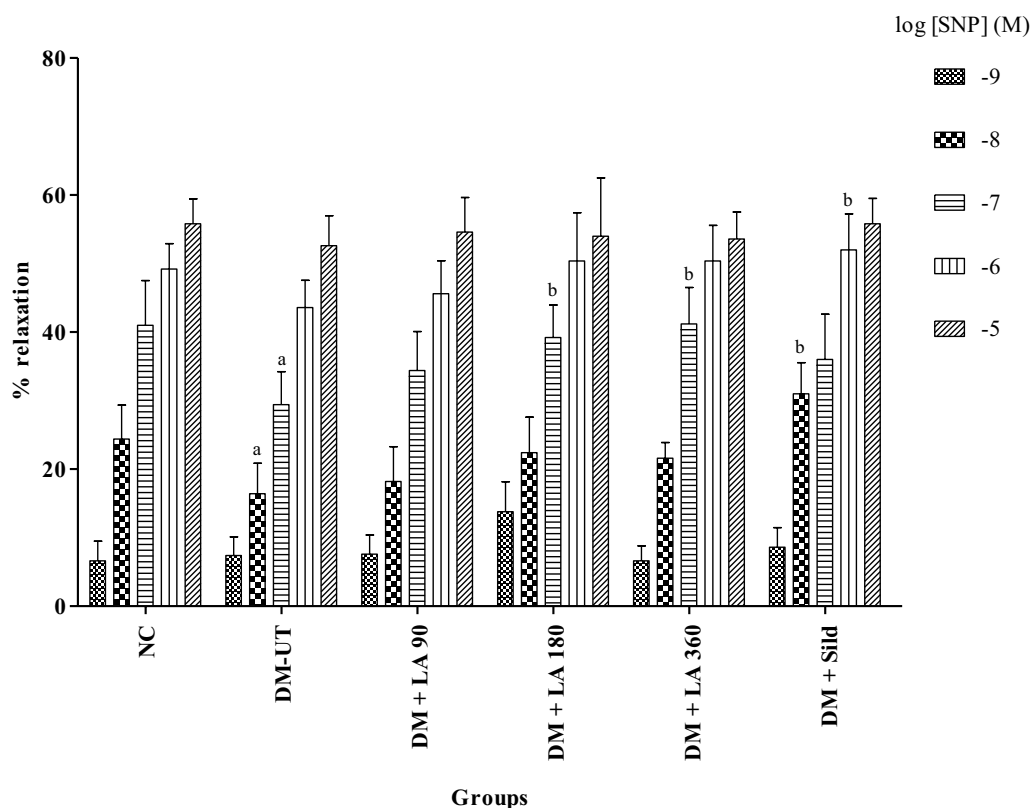
**Fig. 3** Relaxation response of phenylephrine pre-contracted corpus cavernosum to cumulative concentrations of sodium nitroprusside. NC normal control, DM-UT Diabetic untreated, DM + LA 90 diabetic treated with lauric acid (90 mg/kg), DM + LA 180 diabetic treated with lauric acid (180 mg/kg), DM + LA 360 diabetic treated with lauric acid (360 mg/kg), DM + Sild diabetic treated with sildenafil. (a) Significant compared to NC ( $p < 0.05$ ); (b) significant compared to DM-UT ( $p < 0.05$ )

proteins in addition to calcium influx; thus, further amplifying the contraction [27]. This may explain the relatively higher relaxation response to acetylcholine in KCl contracted cavernosal tissues.

In cavernosal tissues pre-contracted with phenylephrine and KCl, this study showed a decline in sodium nitroprusside (SNP) induced relaxation in the diabetic untreated animals. Considering SNP is a nitric oxide (NO) donor, this suggests reduced bioavailability of cGMP, which has been reported to mediate the relaxing action of NO in cavernosal smooth muscles [28]. The improvement in the relaxation response in tissues of diabetic rats treated with lower doses of lauric acid suggests the increase in cGMP activity or amelioration of cGMP signalling. It could also be possibly attributed to inhibition of phosphodiesterase 5 (PDE5); thus reducing the metabolism of the available cGMP and enhancing relaxation. The improvement of relaxation in KCl pre-contracted diabetic cavernosal tissues by all the doses of lauric acid as opposed to only lower doses in phenylephrine contracted tissues, further confirms the possibility of lauric acid inhibiting the depolarizing action of KCl.

Sildenafil, used as the reference drug in this study, is a major standard oral medication for the treatment of erectile dysfunction. Being a phosphodiesterase 5 (PDE5) inhibitor, the actions of sildenafil culminates in sustaining cGMP bioavailability thereby enhancing or prolonging the relaxation of the corpus cavernosum, thus favouring penile erection [8]. This is also further supported by the improvement of relaxation to sodium nitroprusside (SNP) in sildenafil treated diabetic rats. Lauric acid exhibited relative potential in improving the relaxation in cavernosal tissues especially to SNP compared to sildenafil and thus can be explored as an alternative therapy for erectile dysfunction.

Generally, excessive consumption of saturated fatty acids has been associated with increased low-density lipoproteins (LDL) in the circulation, resulting in metabolic and cardiovascular disorders [29]. However, the chain length of lauric acid, being a medium chain fatty acid, may be responsible for the positive effects seen in this study, inspite of its property as a saturated fatty acid. Medium chain fatty acids are more efficiently absorbed into the portal circulation and transported into the



**Fig. 4** Relaxation response of KCl pre-contracted corpus cavernosum to cumulative concentrations of sodium nitroprusside. NC normal control, DM-UT diabetic untreated, DM + LA 90 diabetic treated with lauric acid (90 mg/kg), DM + LA 180 diabetic treated with lauric acid (180 mg/kg), DM + LA 360 diabetic treated with lauric acid (360 mg/kg), DM + Sild diabetic treated with sildenafil. (a) Significant compared to NC ( $p < 0.05$ ); (b) significant compared to DM-UT ( $p < 0.05$ )

liver. They cause an increase in circulating high-density lipoproteins (HDL) which may account for their health benefits [29]. In addition, lauric acid is the most abundant constituent of coconut oil, thus, reputable for its therapeutic properties, especially for diabetes [13] and reproductive disorders [30]. Lauric acid has also been specifically proven to possess vaso-relaxant and antioxidant properties [15]. All these attributes of lauric acid could account for the improved relaxation observed in diabetic rats.

## Conclusion

Lauric acid improved the depressed relaxation of the corpus cavernosum smooth muscles in diabetic male Wistar rats and this could be attributed to the improvement of nitric oxide action and possible inhibition of the depolarization-induced contracting action of KCl. Given the results of this study, it is safe to suggest that lauric acid be incorporated into other well-established management protocols for treatment of erectile dysfunction especially in diabetics.

## Abbreviations

ED: Erectile dysfunction; NO: Nitric oxide; cGMP: Cyclic guanosine monophosphate; PDE5: Phosphodiesterase 5; SNP: Sodium nitroprusside; NaCl: Sodium chloride; KCl: Potassium chloride;  $\text{NaHCO}_3$ : Sodium hydrogen carbonate;  $\text{KH}_2\text{PO}_4$ : Potassium dihydrogen phosphate;  $\text{MgSO}_4$ : Magnesium sulphate;  $\text{CaCl}_2$ : Calcium chloride; S.E.M: Standard error of mean.

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## Author contributions

MVO conceptualised and designed the study under the guidance of HMS. MVO executed the experiments and analysed the data under the guidance of HMS. MVO was responsible for drafting the final manuscript. MUK, MGM, HMS and RAM supervised the study. MUK and MGM were responsible for reviewing the final manuscript. All authors read and approved the final manuscript.

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## Availability of data and materials

The data used to support the findings of this study are available from the corresponding author.

## Declarations

### Ethics approval and consent to participate

Ethical approval was obtained from the Ahmadu Bello University Animal care and use committee with the approval number, ABUCAUC/2017/019. Animals were handled in compliance with the World Medical Association Declaration of Helsinki regarding the ethical conduct of research involving animals.

### Consent for publication

Not applicable.

### Competing interests

All authors declare that they have no competing interests.

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