

Allantoin Alleviates Male Sexual Dysfunction in Diabetic Rats through Augmenting the Level of Testosterone

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ABSTRACT

Objective: A majority of the diabetic patients experience sexual dysfunction. The objective of the study was to investigate the effect of allantoin on sexual dysfunction in diabetic rats. **Methods:** Streptozotocin-induced diabetic Wistar rats were divided into 3 groups: diabetic control group, diabetes + allantoin 100 mg/kg and diabetes + allantoin 200 mg/kg. Diabetic rats were treated with allantoin for 6 weeks and were assessed for its effect on sexual behavior, blood pressure, sperm count, sperm morphology, and levels of glycosylated hemoglobin, serum testosterone, and nitrite. Effects of treatment on diabetic rats were compared with diabetic control rats and normal healthy rats. **Results:** Diabetes decreased sexual behavior, sperm count and levels of serum testosterone and nitrite while increased blood pressure, the level of glycosylated hemoglobin and sperm defects in comparison to healthy rats. After a 6-week treatment period, there was a significant decrease in glycosylated hemoglobin (HbA1C) and blood pressure in the allantoin treatment groups when compared to diabetic control. Also, the rats treated with allantoin performed significantly well in sexual behavioural studies with a significant increase in body weight, sperm count, and levels of serum testosterone and nitrite compared to

diabetic control. **Conclusion:** Oral administration of allantoin improves sexual function in diabetic rats by improving glycemic control and maintaining blood pressure. It also improves sexual function in diabetic rats by preventing the reduction in levels of nitrite and serum testosterone.

Key words: Sexual dysfunction in diabetes, allantoin, testosterone, blood pressure, sperm count

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INTRODUCTION

Diabetes is a chronic metabolic disease characterized by increased blood glucose levels caused either by insulin deficiency or insulin resistance.¹ The number of people with diabetes has increased from 171 million in 2000 to 422 million in 2014 and is expected to increase further in the coming years.² Diabetes is a serious disease which can adversely affect eyes, kidneys, nerves, heart, blood vessels, reproductive organs and sexual function. Erectile dysfunction is a common complication in diabetic men and around 70% of diabetic men sooner or later develop erectile dysfunction (ED).^{1,2,3}

ED is the persistent inability of an individual to achieve and maintain a proper penile erection for a satisfactory sexual performance.³ Millions of people around the world suffer from ED. The main causes of ED include diabetes, endothelial dysfunction associated with hypertension, oxidative stress and a decrease in the level of testosterone among others. Natural products with antioxidant potential have been proven to improve sexual function and ameliorate diabetes-induced sexual dysfunction.^{4,5,6}

Allantoin (ALL) is the active constituent found in yam (sweet potato), plant from *Dioscorea* species.⁷ Allantoin is widely used in the prevention of inflammation and ulcers. It is also reported to have antioxidant activity.⁸ The structure of allantoin resembles that of guanidium derivatives which are known to act by binding to imidazoline receptors. The activation of the isoforms of these receptors i.e. I-1, I-2 and I-3 leads to regulation of blood pressure, increases glucose uptake and regulates insulin release, respectively. Hence it is of special interest to know whether the

activation of these receptors and antioxidant property of allantoin can modulate the complication of diabetes-induced ED.^{9,10,11}

MATERIALS AND METHODS

Materials and chemicals

Streptozotocin (STZ), allantoin, HbA1C kit were purchased from MP Biomedicals, Himedia and Coral Clinical Systems in India, respectively. All other chemicals used in the study were of analytical grade.

Animals

Twelve weeks old male Wistar albino rats weighing between 250-300 g were obtained from Central Animal House, Al-Ameen College of Pharmacy, Bengaluru, India. The animals were housed in polypropylene cages on clean paddy husk bedding. Animals were kept in an environment with the controlled temperature at 25±2°C and exposed to 12 h light/dark cycle. All animals were provided with pellet and water *ad libitum*. All the experiments were performed under anesthesia and care was taken to minimize pain to animals. The protocol for the animal experiment was approved by the institutional animal ethical committee. Approval number: AACP/IAEC/JAN2016/04.

Induction of diabetes and experimental groups

Diabetes was induced by administering STZ (52 mg/kg, i.p.) in freshly prepared 0.1 M ice-cold sodium citrate buffer pH (4.5).¹¹ A 5% glucose solution was given to rats 24 h after STZ injection for one day to prevent

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hypoglycemic shock. Seventy-two hours after the injection of STZ, fasting blood glucose levels were estimated by glucose kit. The animals with fasting blood glucose more than 250 mg/dL were considered diabetics, and were divided into 3 groups (group 2-4). Group 2 was considered as diabetic control (DC) and was administered with the vehicle. Group 3 and 4 were treated with allantoin at a dose of 100 and 200 mg/kg p.o. respectively for 6 weeks. A group of normal rats was taken and kept as normal control (group 1 or NC). All the groups contained 6 animals each.

Effect of allantoin on sexual behavioral of diabetic rats

Before induction of diabetes, the male rats were trained for sexual activity in the presence of estrous ovariectomized female rats. For the sexual behavioral study, the female rats were ovariectomized and treated with diethylstilbestrol (1 mg/kg, p.o., administered 48 h prior to sexual behavior study) and progesterone (5 mg/kg, s.c., administered 4 h prior to the sexual behavior study) to induce artificial estrous phase. For sexual activity, a male rat was first introduced in the sexual behavior study chamber and was let to acclimatize to the environment for 5-10 min and then the female rat was introduced and the following parameters were evaluated.^{12,13}

- Mount latency (ML): time from the introduction of a female into the study chamber up to the first mount.
- Intromission latency (IL): time from the introduction of the female into the study chamber up to the first intromission by the male.
- Mount frequency (MF): Number of mounts in a sexual cycle before ejaculation.
- Intromission frequency (IF): Number of intromission in a sexual cycle before ejaculation.
- Ejaculation latency (EL): time from the first intromission to the ejaculation.
- Post-ejaculatory interval (PEI): time from end of the first ejaculation to start of next intromission.

Effect of allantoin on body weight in diabetic rats

The weight of each animal was measured at the end of every week to monitor the general health of the animal. The weight was taken before the induction of diabetes and continued until the end of the study.

Effect of allantoin on blood pressure in diabetic rats

Thirty minutes after behavioral studies, blood pressure was measured using AD Instrument non-invasive blood pressure system (Australia). The animals were allowed to calm down after sexual behavior study before measuring blood pressure. Animals were also trained earlier to accustom to the animal holder before measuring blood pressure. The blood pressure was analyzed using PowerLab LabChart software version 7.

Effect of allantoin on level of glycosylated hemoglobin in diabetic rats

Whole blood was collected in EDTA containing micro centrifuge tubes and mixed slowly. Erythrocytes were separated and lysed to collect hemoglobin. The level of HbA1C was determined using commercial kit purchased from Coral Clinical Systems Goa, India.

Effect of allantoin on level of nitrite and testosterone in diabetic rats

Blood samples were also collected in microcentrifuge tube without anticoagulant, allowed to stand for 15 min at room temperature and then centrifuged to separate serum which was stored at -20°C. The assay was carried out by adding 100 µL of the serum and 100 µL of the Greiss reagent in a 96 well culture plate. The mixture sample was then incubated for 30 minutes and the absorption was measured at 570 nm in a UV-visible spectrophotometer. The amount of nitrite in serum samples was determined by comparison with a NaNO₂ standard curve.¹⁴

Testosterone in serum was estimated using the procedure mentioned by the manufacturer of enzyme-linked immune sorbent assay (ELISA) kit. The kit was purchased from Abcam®, USA.

Effect of allantoin on sperm count and defects

At the end of sexual behavioral study, the rats were sacrificed with large dose of ether anesthesia and the epididymal tail was trimmed with scissors and placed in Petri dishes containing 1.0 mL of 0.1 M phosphate buffer of pH 7.4, it was gently swirled for homogeneity and to allow sperm diffusion in the solution for 10 min under 37°C for dispersion of sperm cells. These were assessed for the number and gross morphology.¹⁵ For sperm motility, an aliquot of 10 µL was placed in a hemocytometer chamber and analyzed under a light microscope. One hundred sperm were evaluated per animal and classified into motile and immotile.¹⁶

$$\text{Number of sperms per caudal epididymis} = \frac{\text{Mean count} \times 50 (\text{total volume})}{0.01 \times 0.01 (\text{volume of counting chambers})}$$

$$\text{Defective sperm \%} = \frac{\text{total number of defective sperm}}{\text{total number of sperms counted}} \times 100$$

For gross morphology, 0.05 mL of 1% eosin yellow solution was added to the sperm suspension and 10 µL of this was taken on a glass slide and the gross morphology per 100 sperms was visualized.

Statistics

One-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test was employed to evaluate statistical significance. Values are presented as mean ± standard error of the mean (SEM) of 6 readings. Statistical calculation was performed using Prism version 5 (GraphPad Inc, CA, USA). A *p* value < 0.05 was considered as statistically significant.

RESULTS

Allantoin augments sexual function of diabetic rats

Sexual function in diabetic control rats was significantly reduced when compared to normal control rats, after 6 weeks of induction of diabetes. Treatment with allantoin increased sexual function of diabetic rats in comparison to diabetic control rats. This effect on all parameters of sexual function studied was dose-dependent except for intromission latency (Table 1).

Allantoin prevents loss in body weight of diabetic rats

Normal control rats gained 12% of body weight while diabetic rats lost approximately 15% of body weight during the experimental period. Treatment with allantoin at 100 mg/kg and 200 mg/kg increased the weight of diabetic animals up to 3% and 7%, respectively.

Allantoin decreases hypertension in diabetic rats

Blood pressure was significantly increased in rats after 6 weeks of induction of diabetes. Treatment with allantoin decreased diabetes-induced hypertension significantly when compared to vehicle treated diabetic rats (Figure 1).

Allantoin decreases level of glycosylated hemoglobin in the diabetic rats

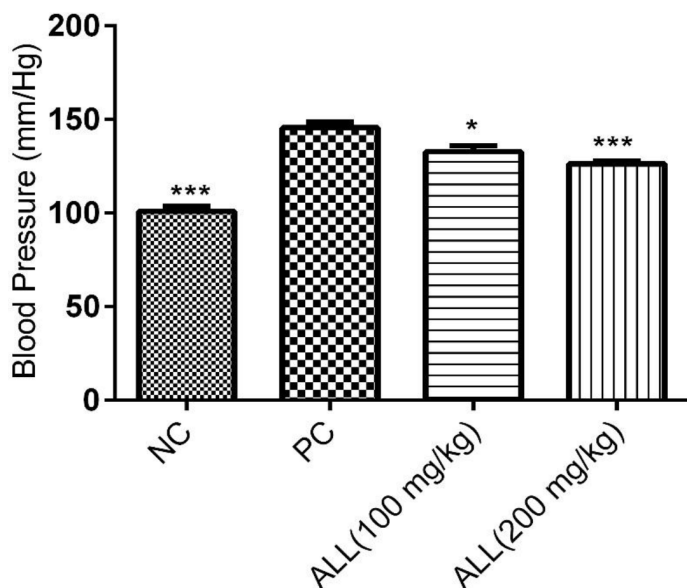
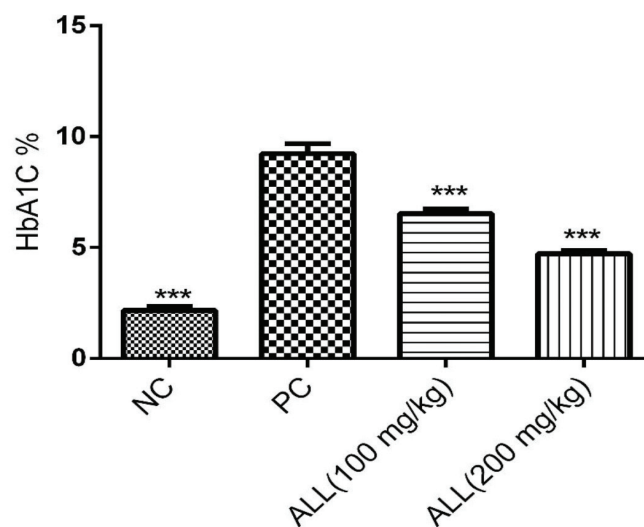
As expected, the level of glycosylated hemoglobin was more in diabetic rats in comparison to healthy rats. Treatment with allantoin decreased the level of glycosylated hemoglobin in diabetic rats though the level of glycosylated hemoglobin was still higher than healthy rats (Figure 2).

Allantoin increases the level of nitrite and testosterone in the serum of diabetic rats

The level of nitrite in the serum of diabetic rats was significantly decreased in comparison to normal control rats. Treatment with allantoin

Table 1: Effect of oral administration of allantoin on sexual behavior in diabetic rats. All values are expressed as mean \pm SEM, n=6, **p<0.01, ***p<0.001 when compared to diabetic control group by using One-way Analysis of Variance (ANOVA) followed by Tukey's multiple comparison test.

Parameters	Normal Control	Diabetic Control	Allantoin (100 mg/kg, p.o.)	Allantoin (200 mg/kg, p.o.)
MF (number of times)	4.5 \pm 0.2***	1.9 \pm 0.3	3.7 \pm 0.0***	4.2 \pm 0.0***
IF (number of times)	6.3 \pm 0.0***	3.6 \pm 0.0	5.9 \pm 0.0***	6.9 \pm 0.0***
ML (s)	159.9 \pm 0.6***	256.2 \pm 0.1	170.6 \pm 0.1***	151.8 \pm 0.5***
IL (s)	200.2 \pm 0.2***	319.5 \pm 0.6	188.3 \pm 0.9***	211.1 \pm 2.1***
EL (s)	317.0 \pm 0.5***	237 \pm 0.9	282.7 \pm 0.6**	368.2 \pm 18.2***
PEI (s)	470.1 \pm 1.0**	601.4 \pm 0.5	485.2 \pm 1.0**	411.2 \pm 1.1**

**Figure 1:** Effect of oral administration of allantoin on blood pressure in diabetic rats. One way ANOVA followed by Tukey's multiple comparison test was used for evaluating statistical significance. All values are expressed as mean \pm SEM, n=6, *p<0.05, ***p<0.001 when compared to the diabetic control group. NC: Normal control, PC: Positive / diabetic control.**Figure 2:** Effect of oral administration of allantoin on level of glycosylated hemoglobin in diabetic rats. One-way ANOVA followed by Tukey's multiple comparison test was used for evaluating statistical significance. All values are expressed as mean \pm SEM, ***p<0.001 when compared to the diabetic control group. NC: Normal control, PC: Positive /diabetic control.

in minimized the decrease in the level of nitrite in the serum of diabetic rats (Figure 3A).

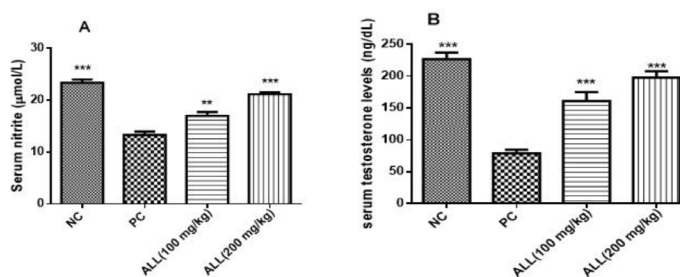
The level of testosterone was significantly decreased in diabetic rats in comparison to the level of this hormone in age-matched healthy control rats. Six weeks after treatment of allantoin, the level of male sex hormone was significantly elevated in diabetic rats when compared with diabetic rats which did not receive allantoin (Figure 3B).

Allantoin increases sperm count, and decreases the level of dead sperm and defective sperm in diabetic rats

The sperm count of diabetic control rats was significantly lower, and the level of the dead and defective sperms was significantly higher when compared to normal control rats. Treatment of allantoin increased sperm count, and decreased the level of dead and defective sperm in diabetic animals in comparison to normal control rats (Figure 4).

DISCUSSION

Diabetes induces a host of pathological changes in the body which includes endothelial dysfunction and a decrease in the level of hormones

**Figure 3:** Effect of oral administration of allantoin on the level of nitrite (A) and testosterone (B) in diabetic rats. One-way ANOVA followed by Tukey's multiple comparison test was used for evaluating statistical significance. All values are expressed as mean \pm SEM, n=6, **p<0.01, ***p<0.001 when compared to the diabetic control group. NC: Normal control, PC: Positive / diabetic control.

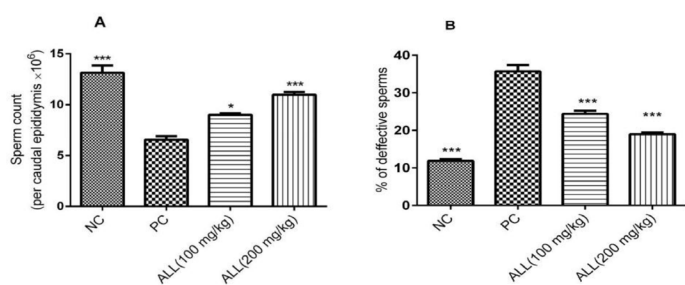


Figure 4: Effect of oral administration of allantoin on sperm count (A) and level of defective sperm in diabetic rats (B). One-way ANOVA followed by Tukey's multiple comparison test was used for evaluating statistical significance. All values are expressed as mean \pm SEM, n=6, *p<0.05, ***p<0.001 when compared to diabetic control group. NC: Normal control, PC: Positive / diabetic control.

(testosterone) and enzymes (nitric oxide synthase). These changes are responsible for the development of sexual dysfunction including erectile dysfunction.¹⁶⁻²⁰ In addition, decrease in sperm count and increase in defects of sperm abnormality due to diabetes hampers reproductive health. Here, we show that allantoin decreases the level of glycosylated hemoglobin and decreases hypertension, and increases the level of testosterone and nitrite, a metabolite of nitric oxide in serum. These changes help in elevation of sexual function in diabetic rats.

Diabetes is an established risk factor for the development of ED and has been associated with sexual dysfunction both in men^{21,22,23} and women.^{24,25,26} A threefold increase in the risk of ED has been documented in diabetics when compared with nondiabetic men.^{21,22,23} In animal model also diabetes decreases sexual function.^{6,18} Namely, sexual desire was decreased as evident from the increase in ML and IL. Erectile function was also decreased as evident from the decrease in IF and increase in PEI.^{6,13,18} Treatment of allantoin increased the sexual function in diabetic rats. This could be due to an increase in endothelial function which was evident from the decrease in hypertension.

Endothelial dysfunction is associated with the development of hypertension and increasing endothelial dysfunction has been the goal of anti-hypertensive therapy. Hypertension and cardiovascular disease are risk factors for male erectile dysfunction (ED).²⁷ The incidence of ED is associated with the severity and duration of hypertension.²⁸ Hypertension is often associated with aberrant smooth muscle cell proliferation in the systemic vasculature and this is thought to be responsible, in part, for the reduction in the lumen of the blood vessel. Such increase in smooth muscle cells could adversely decrease the erectile response by reducing the blood flow into the cavernous sinuses which is required for initiation of erection. Abnormal cell growth also reduces the compliance of the cavernous sinus thus leading to a defect in the veno-occlusive mechanism required for the maintenance of erection. Allantoin decreased hypertension in treated diabetic mice in comparison to diabetic control mice suggesting its role in ameliorating endothelial dysfunction. Endothelial dysfunction is also associated with hyperglycemia as in diabetes.

The pathogenesis of ED in diabetes is due to poor glycemic control i.e. elevated level of sugar in the blood and HbA1C.^{18,23} A better glycemic control was achieved in diabetic rats treated with allantoin than the diabetic control group. The chronic hyperglycemia condition results in endothelium dysfunction that is manifested as the decreased bioavailability of nitric oxide (NO) due to the decrease in the expression of nitric oxide synthase (NOS) which generates it. NO is one of the major neurotransmitters responsible for penile erection. After release from endothelial and nerve cell, NO diffuses into the penile smooth muscle to activate soluble guanylate cyclase which increases the level of cyclic

guanosine monophosphate. This second messenger phosphorylates ion channels and decreases the inflow of calcium required for contraction of the penile smooth muscle. Coordinated relaxation of penile smooth and penile arteries results in persistent penile erection required for sexual activity.^{6,12,13,15,18} Interestingly, testosterone, a male sex hormone stimulates and maintains the NOS.²⁹⁻³¹ We estimated nitrite, the stable metabolite of NO in the serum of rats. Nitrite can be converted to NO *in vivo* and is an alternate source of NO.^{32,33} While estimating serum nitrite levels in diabetic rats, we observed that the rats treated with allantoin had higher levels of serum nitrite which implies an increase in the level of nitric oxide in the serum. This may infer an increase in the expression and / activity of NOS in the allantoin treated groups as compared to untreated diabetic rats.

The decrease in the level of testosterone is a risk factor for sexual function. Hypogonadism or subnormal testosterone concentrations have been found in 25% of men with diabetes in association with inappropriately low luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations.^{34,35,36} Testosterone regulates nearly every component of erectile function, from pelvic ganglions to smooth muscle, and to the endothelial cells of the corpora cavernosa. It also modulates the timing of the erectile process, which occurs as a function of sexual desire, coordinating penile erection for the sexual activity. From the results, we noticed that the treatment groups had better levels of serum testosterone in comparison with diabetic control group.

Oligospermia may or may not have a relation with ED but its negative effect on fertility has been established. The result from this study shows that there was a reduction in the sperm count in the diabetic control group. Additionally, we observed an increase in the percentage of defective sperm in the diabetic group. Allantoin administration increased the sperm count and reduced the percentage of defective sperm, this might be probably due to the antioxidant effect of allantoin and its ability to elevate the serum testosterone levels.

In summary, multiple pathways are altered in diabetes-induced sexual dysfunction.³⁷ It is associated with an increase in blood pressure and a decrease in the level of nitrite and testosterone. Allantoin treatment decreased the level of hypertension and increased the level of nitrite and testosterone in diabetic rats. Allantoin increased the sperm count and decreased the level of defective sperm in diabetic rats. This might increase the reproductive function of a male in diabetes. Allantoin is effective as a curative agent in diabetes-induced ED of rats. Clinical studies need to be conducted to evaluate its usefulness in diabetic male subjects. We also suggest that further molecular pharmacologic studies need to be performed for elucidating the mechanism through which allantoin exhibits the protective effect in diabetes-induced ED.

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CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

ABBREVIATIONS USED

ALL: Allantoin; **dL:** Deciliter; **EL:** Ejaculation latency; **HbA1C:** Glycosylated hemoglobin; **IL:** Intromission Latency; **IF:** Intromission Frequency; **NO:** Nitric oxide; **ML:** Mount Latency; **MF:** Mount frequency; **PEI:** Post-ejaculatory interval; **STZ:** Streptozotocin; **NC:** Normal control; **PC:** Positive/diabetic control.

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