Ameliorative effects of *Lycium chinensis* on male sexual dysfunction and testicular oxidative damage in streptozotocin-induced diabetic rats

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Abstract The root bark of *Lycium chinense* (LC) has been reported to have potent antioxidant and antidiabetic properties. In the present study, we investigated the attenuative effect of LC against diabetes induced sexual dysfunction and testicular damages in animal models. Diabetic animals were treated with LC (100 and 400 mg/kg) once daily for 6 weeks. At the end of the treatment, mating behavior tests were performed and the animals were sacrificed for the determination of hormonal profile, oxidative stress indices and sperm analysis. LC administration significantly decreased blood glucose level, enhancement of the antioxidant enzyme activities, restored altered sperm characteristics and markedly improved levels of luteinizing hormone, follicle-stimulating hormone and testosterone as compared to the untreated diabetic animals. Furthermore, LC also improved sperm count, viability, motility, increased the reproductive organs weight. The results obtained indicated that *L. chinense* has beneficial effects in diabetes sexual dysfunction.

Keywords *Lycium chinensis* · Oxidative stress · Spermatogenic dysfunction · Antioxidant · Diabetes mellitus

Introduction

Diabetes mellitus is a lifelong metabolic disease which bears a hallmark of hyperglycemia due to deficiency in the action of insulin, insulin secretion or both. Reproductive dysfunction is one of the several diabetic complications affecting about 90% of diabetic patients (Bener et al., 2009; Isidro, 2012). Some of the reproductive dysfunction experienced in diabetic situation includes testicular dysfunction, decreased fertility, reduced spermatogenesis, production of dysfunctional sperm and retrograde ejaculations (Mohamed et al., 2018). Oxidative stress, increased free radicals generation and impaired antioxidant defense mechanisms has been implicated in the pathogenesis of reproductive dysfunction in diabetes mellitus (Shi et al., 2017; Shrilatha and Muralidhara, 2007). Therefore, substances with antioxidant effect may be a possible remedy in mitigating the adverse effect of diabetes and its associated sexual dysfunction (Thakur et al., 2009).

Lycium chinense (family Solanaceae) popularly known as Chinese boxthorn is famous for its application as a functional food and medicine in many Asian countries especially China. The root bark of *L. chinense* (popularly referred to as Cortex Lycii) has a long history of treating several diseases such as diabetes, cough and inflammatory disorders (Yao et al., 2011). Several bioactive constituents are richly found in the root bark of *L. chinense*, flavonoids, phenolics, cyclopeptides, and phenolic glycosides (Chen et al., 2017). Previous findings have attributed actions such as neuroprotection, antioxidant, anti-inflammatory,

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antiulcer and anti-obesity activities to *L. chinense* (Chen et al., 2016; Olatunji et al., 2016). The antidiabetic action of *L. chinense* have been previously reported in pancreatic beta cells and obese-diabetic rats (Wang and Ye, 2016; Ye et al., 2008). On the basis of these previous findings, we envisaged that *L. chinense* might have the potentials of improving diabetic induced sexual dysfunction. Thus, this study investigated the protective effects of the root bark of *L. chinense* (LC) on male sexual dysfunction and testicular oxidative damage in streptozotocin-induced diabetic rats.

Materials and methods

Plant collection

Lycium chinense was collected at Dongtai, Jiangsu Province, China and was identified at the School of Pharmacy Jiangsu University, China where the reference specimen was deposited.

Preparation of plant material

The root bark of *L. chinense* was refluxed with 95% ethanol for 4 h and the extract was concentrated with a rotary evaporator. The ethanolic extract was preserved at 4 °C until further use.

Animals

Wistar rats (150–220 g) were housed in cages and kept under suitable controlled environment (temperature; 23 ± 2 °C; relative humidity; 40–55%). The rats were acclimatized for 7 days and were allowed access to food and water ad libitum. The protocols for the animal experiment were in line with the guidelines for the care and use of laboratory animals of the National Institutes of Health. Ethical approval was obtained from the Ethics Committee on the Use of Animals (UJS-LAER-2017112101).

Induction of diabetes

Overnight fasted rats were intraperitoneally administered with a single injection of freshly prepared streptozotocin (in sodium citrate buffer; pH 4.5, 65 mg/kg). Seventy hours after streptozotocin injection, fasting blood glucose level of the rats was measured using a glucometer. Rats having blood sugar level ≥ 250 mg/dL were adjudged as diabetic and were used for further studies.

Experimental design

The diabetic animals were divided into five groups of six rats per group; Group I is the normal control group treated with distilled water; Group II is the diabetic treated with distilled water, Groups III and IV were treated with LC (100 and 400 mg/kg, respectively); Group V was the positive control group and treated with Sildenafil citrate (5 mg/kg), an approved oral therapy for the treatment of erectile dysfunction. The extract and drug were administered by oral gavage for 6 weeks.

Copulatory behavior test

The mating behavior test behavioral test adopted the previous method of Suresh and Prakash (2012). Female rats were ovariectomised and made sexual receptivity by administering 10 µg/0.1 mL of 3-benzoyloxy-17β-estrol (subcutaneously) 48 h before testing and 500 µg progesterone in 0.1 mL sesame oil 4 h prior to the sexual behavioral test (Nusier et al., 2007). Normal and diabetic male rats that have been treated were kept in cages under dim red light and each male rat was allowed 10 min of adaptation period before pairing the sexually receptive female rats with the male rats in the cages on a one to one basis. The sexual training activity was terminated if any of the male or female rats failed to initiate sexual activity. After the placement of the female rats, the following male mating behaviors were evaluated: Intromission latency (IL): is the time of the introduction of the female until the first intromission by the male, Post- ejaculatory interval (PEI): is the time interval between first ejaculation until the next intromission; Mount latency (ML): is the time interval of the introduction of the female until the first mount by the male and Ejaculation latency (EL): is the of the first intromission until ejaculation. The test was performed on day 42 after administration of LC and the positive control drug.

Blood, semen and tissue sampling

After the treatment and experimentation period, the male rats were anaesthetized and sacrificed by cervical dislocation. The blood samples, testes and epididymis of the rats were collected for biochemical estimation. The serum obtained from the blood sample was used for the determination of levels of male reproductive hormones (follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone) with the aid of a commercially available ELISA kit (Wuhan Fine Biological Technology, Wuhan, Hubei, China and ERBA Fertikit, Germany). The testes of each rat were immediately excised and weighed and homogenized in ice cold saline, centrifuged at 2500g for

15 min which was used for the assessment of markers of oxidative stress namely reactive oxygen species (ROS), malondialdehyde (MDA), superoxide dismutase (SOD), glutathione (GSH) and catalase (CAT) using ELISA kit based on the instruction of the manufacturers manual (Nanjing Jiancheng Bioengineering Institute, Nanjing, China).

Sperm analysis

Sperm analysis was determined based on previously described method (Suresh and Prakash, 2012). The percentage of sperm motility was evaluated according to the method of Sonmez et al. (2005), while the percentage of sperm viability was evaluated by using eosin-nigrosin stain based on previous method (Kose et al., 2012).

Statistical data analysis

Values were expressed as mean $\pm$ SD ($n = 6$). One way Analysis of Variance (ANOVA) followed by Tukey Post hoc multiple comparison test was used for statistical analysis. Statistical significant difference was considered at $p < 0.05$. Analyses was accomplished using SPSS statistical software (version 16.0, SPSS Inc. Chicago, Illinois, USA).

Results and discussion

L. chinense decreases fasting blood glucose levels in diabetic rats

The intraperitoneal administration of streptozotocin led to a state of hyperglycemia, which is a distinct feature of diabetes mellitus. Streptozotocin induces the generation of ROS resulting in insulin-dependent diabetes due to the selective destruction of beta cells (Lenzen, 2008). It was observed that after 6 weeks of administering *L. chinense* extract, the blood sugar levels was markedly decreased in

comparison with the non-treated diabetic group (Table 1). The untreated diabetic rats suffered from consistent alteration in blood glucose level, which increased over time during the course of the study. The blood sugar level in the non-treated diabetic rats was approximately three fold higher than the normal control rats. The administration of *L. chinense* led to a significant reduction in the blood glucose levels of the treated diabetic rat group in a concentration dependent manner (Table 1).

L. chinense increases body and testes weights in treated diabetic rats

The decline in the body weight is one of the obvious signs of poor glycemic control experienced in diabetes mellitus. The non-treated diabetic animals had significantly observable mean body weight reduction as compared to the non-diabetic control rats (Table 1). The mean final body weight of the control rats was 305.76 ± 11.07 g. Diabetic rats had mean final body weight of 158.46 ± 7.20 g. In contrast, the administration of *L. chinense* significantly increased the body weight of the treated diabetic rats when compared to the non-treated diabetic control rats. Furthermore, the results displayed in Table 1 indicated that the diabetic rats had a significant reduction in the testes weight of as compared to the normal control. After the administration of *L. chinense*, the reduced weight of testes in the treated diabetic rats was markedly increased in comparison with the untreated diabetic rat group.

L. chinense upregulated the antioxidant defense system in testis of diabetic rats

Accumulating evidences have continuously implicated oxidative stress as a critical parameter responsible for the pathophysiology of diabetic complication including spermatogenic dysfunction (Khaki et al., 2010; Kanter et al., 2013; Walczak-Jedrzejowska et al., 2013). The over production of ROS as well as the depletion of the antioxidants enzymes in the testicular tissues leads to a cascade of

Table 1 Effect of LC on FBG, body weight and testis weight in diabetic rats

Group (mg/kg)	Fasting blood glucose (mg/dL)	Final body weight (g)	Testis weight (g)
NC	115.50 ± 2.65	305.76 ± 11.07	1.57 ± 0.21
DC	$429.10 \pm 10.09^{\#}$	$158.46 \pm 7.20^{\#}$	$0.93 \pm 0.08^{\#}$
LC 100	$308.25 \pm 6.41^*$	$197.03 \pm 8.44^*$	$1.17 \pm 0.14^*$
LC 400	$189.70 \pm 5.11^*$	$258.60 \pm 11.18^*$	$1.37 \pm 0.26^*$
SC5	$205.25 \pm 6.90^*$	$233.94 \pm 12.00^*$	$1.19 \pm 0.19^*$

Values are expressed as mean $\pm$ SD ($n = 6$)

NC normal control group, DC diabetic control, LC 100 *Lycium chinense* 100 mg/kg, LC 400 *Lycium chinense* 400 mg/kg, SC 5 Sildenafil citrate 5 mg/kg

$^{\#}p < 0.05$ as compared to normal control, $^*p < 0.05$ when compared to diabetic control

cytotoxic process which damages the proteins, unsaturated fatty acids and the nucleic acids of the spermatozoa plasma membrane (Khaki et al., 2010; Shi et al., 2017). Endogenous antioxidant enzymes are vital in maintaining proper antioxidant defense in the testicular tissues by protecting against ROS and oxidative stress (Fujii et al., 2003). Oxidative damage in the diabetic induced rats was evaluated by the determination of ROS, MDA and antioxidant enzymes SOD, GSH and CAT. MDA levels is increased in several tissues and endogenous antioxidant enzymes levels are diminished in diabetic conditions (Oladipo et al., 2018; Zhao et al., 2017). In addition, a number of prior studies confirmed the negative effect of oxidative stress in the testis of diabetic rats by inducing apoptotic cell death of the testicular tissue (Baynes and Thorpe, 1999; Cai et al., 2000). The levels of oxidative stress markers namely MDA, ROS and the antioxidant enzymes GSH, CAT and SOD activities in the testes of non-treated diabetic animals are depicted in Fig. 1. The antioxidant enzyme levels in the testis of non-treated diabetic animals was observed to be significantly downregulated in comparison to the normal non diabetic rats, while the MDA and ROS levels showed an opposite pattern as revealed by their significantly higher levels as compared with the non-diabetic control rats. *L. chinense* significantly reduced the elevated levels of MDA and ROS levels in the testis of treated diabetic rats. In addition, the reduced levels of CAT, GSH and SOD in the testis of diabetic rats were significantly upregulated in a concentration dependent fashion after the administration of *L. chinense*. This study indicated that administering *L.*

chinense extract to the diabetic rats attenuated testicular tissue damage by preventing against ROS generation and upregulating the endogenous antioxidant diabetic treated rats.

L. chinense increases hormone levels in the serum of diabetic rats

In diabetes, the levels of testosterone is reduced due to the reduction in insulin secretion which impedes the production of FSH and LH. These hormones are responsible for the stimulation of the production of androgens such as testosterone. Testosterone regulates spermatogenesis, the activities of sertoli cell, testes weight and the male phenotype (Dkhil et al., 2016; Pitteloud et al., 2005). The non-treated diabetic rats had significantly reduced levels of serum hormonal profiles (testosterone, FSH and LH) as compared to the non-diabetic normal control rats. *L. chinense* at the treatment doses induced a marked elevation of serum testosterone, FSH and LH levels when juxtaposed with the non-treated diabetic rats. These increase was observed to correspond to the administered concentration (Table 2).

L. chinense increases sperm parameters in diabetic rats

Spermatogenesis is a vital function of the testes and previous studies have indicated that hyperglycemia impairs the quality, shape, form and structure of the sperm

Fig. 1 Effect of *L. chinense* on oxidative stress parameters (A) ROS, (B) MDA, (C) GSH, (D) SOD, (E) CAT activities in streptozotocin induced diabetic rats. Values are expressed as mean $\pm$ SD (n = 6). * p < 0.05 compared with the diabetic control group; # p < 0.05

compared with the normal control group. NC normal control group, DC diabetic control, LC 100 *Lycium chinense* 100 mg/kg, LC 400 *Lycium chinense* 400 mg/kg, SC 5 Sildenafil citrate 5 mg/kg

Table 2 Effect of LC on hormonal profile in diabetic rats

Group (mg/kg)	Testosterone (ng/mL)	FSH (ng/mL)	LH (ng/mL)
NC	4.08 ± 0.35	6.08 ± 0.42	7.08 ± 0.89
DC	1.84 ± 0.15 [#]	3.49 ± 0.51 [#]	5.37 ± 1.05 [#]
LC 100	2.74 ± 0.29*	4.05 ± 0.47*	5.93 ± 1.07*
LC 400	3.59 ± 0.42*	4.88 ± 0.38*	6.44 ± 1.17*
SC 5	2.19 ± 0.36	3.61 ± 0.22	5.52 ± 0.38

Values are expressed as mean ± SD (n = 6)

LH luteinizing hormone, FSH follicle stimulating hormone, NC normal control group, DC diabetic control, LC 100 *Lycium chinense* 100 mg/kg, LC 400 *Lycium chinense* 400 mg/kg, SC 5 Sildenafil citrate 5 mg/kg

[#]*p* < 0.05 as compared to normal control, **p* < 0.05 when compared to diabetic control

Table 3 Effect of LC on sperm parameters in diabetic rats

Group (mg/kg)	Sperm count (millions/mL)	Sperm viability (%)	Sperm motility (%)
NC	121.40 ± 7.01	67.05 ± 3.11	45.38 ± 3.09
DC	49.82 ± 5.27 [#]	34.90 ± 1.82 [#]	17.41 ± 2.33 [#]
LC 100	60.48 ± 4.92*	42.77 ± 2.02*	24.17 ± 0.14*
LC 400	89.33 ± 6.08*	54.28 ± 2.80*	35.37 ± 4.42*
SC 5	51.00 ± 3.07	39.16 ± 1.99	20.10 ± 5.04

Values are expressed as mean ± SD (n = 6)

NC normal control group, DC diabetic control, LC 100 *Lycium chinense* 100 mg/kg, LC 400 *Lycium chinense* 400 mg/kg, SC 5 Sildenafil citrate 5 mg/kg

[#]*p* < 0.05 as compared to normal control, **p* < 0.05 when compared to diabetic control

Fig. 2 Effect of *L. chinense* on male sexual behaviour in diabetic rats (A) mount latency, (B) mount frequency, (C) ejaculatory latency, (D) intromission latency, (E) post ejaculatory interval in streptozotocin induced diabetic rats. Values are expressed as mean ± SD (n = 6). **p* < 0.05 compared with the diabetic control group;

[#]*p* < 0.05 compared with the normal control group. NC normal control group, DC diabetic control, LC 100 *Lycium chinense* 100 mg/kg, LC 400 *Lycium chinense* 400 mg/kg, SC 5 Sildenafil citrate 5 mg/kg

(Agarwal et al., 2014; Khaki et al., 2010). Furthermore, the thickness of the basal lamina in somniferous tubules is increased during diabetes leading to reduction in the production of sperm (Rohrbach and Martin, 1982). As shown

in Table 3, sperm motility, sperm count and sperm viability were significantly reduced in non-treated diabetic rat group indicating impaired spermatogenesis. However, diabetic rat group administered with *L. chinense* exhibited significant

upregulation and reversed the decline in the sperm parameters in the treated diabetic rats (Table 3).

***L. chinense* improves male sexual behaviour in diabetic rats**

Alterations in male sexual parameters such as ML, EL, PEI, IL and MF in diabetic rats suggest an impairment in sexual performance (De et al., 2016). Sexual motivation is evaluated by a decrease in mount latency and intromission latency (Yakubu et al., 2005). The diabetic rat group that were treated with *L. chinense* had increased male sexual activities which was significant when compared to the non-treated diabetic rats. These was evident in the improvement in MF and a decline in EL, PEI, ML and IL in the groups of diabetic rats administered with *L. chinense*. As for the diabetic rats, decrease in sexual behavior was observed by noticeable decline in MF and increase in EL, PEI, IL and ML (Fig. 2).

Diabetes mellitus is rapidly becoming one of the foremost severe metabolic disorder. The increasing number of secondary complications such as neuropathy, nephropathy, retinopathy, cardiovascular diseases, limb amputation and sexual dysfunction that accompanies diabetes is mainly responsible for the impairment of numerous organs and functions of the organism leading to morbidity and mortality (El Rabey et al., 2017). Diabetes induced reproductive disorder is one of serious secondary complication of diabetes which adversely affects the quality of life of patients. Medicinal plant have been in existence for thousands of years as a mean of preventing and treating several chronic disorders including diabetes. The root bark of *L. chinense* is a famous traditional Chinese medicine (TCM) with several health enhancing properties. It has a long history of been used in TCM as an antidiabetic agent.

In conclusion, this present study demonstrated that *L. chinense* attenuated impaired male sexual dysfunction in diabetic rats by significantly increasing testes weight, spermatogenic quality and quantity and upregulating the antioxidant enzyme status by way of decreasing oxidative stress. These findings suggest the possible use of *L. chinense* in the enhancement or protection against diabetic induced sexual dysfunction.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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