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Methanolic Extract of *Maytenus Procumbens* Roots Ameliorates Erectile Dysfunction in Fructose-Streptozotocin Induced Type 2 Diabetes in Rats

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Abstract

Erectile dysfunction (ED) due to diabetes mellitus remains difficult to treat despite advances in pharmacotherapeutic approaches in the field. Therefore, this study investigated the erectogenic effect of the methanolic extract of *Maytenus procumbens* on type 2 diabetes in rats. The fructose-streptozotocin model was used to induce type 2 diabetes-linked ED in male rats. The sexually active rats were randomly divided into two major groups; normal group and high fructose fed group for 120 days. After 120 days, the high fructose fed group rats were given a single intraperitoneal injection of a freshly prepared streptozotocin solution (30 mg/kg).The diabetic ED rats were orally administered with the extract at 250 mg/kg, daily for 28 days. The serum, brain and penile tissues were removed for biochemical analysis and protein expression. Increased testosterone level, mounting frequency, reduced blood glucose level and serum fructosamine content were observed after 28 days of treatment in diabetic rats. Methanolic extract also exhibited an inhibitory effect on arginase, AChE and ACE activities. The crude extract further downregulated proteins PDE-5, RhoA and increased expression of eNOS in the diabetic ED treated rats. The results obtained indicate that the methanolic extract of *Maytenus procumbens* roots ameliorates erectile dysfunction in type 2 diabetic induced erectile dysfunction in rats.

Keywords: Erectile dysfunction; Phosphodiesterase-5; cyclic guanosine monophosphate; *Maytenus procumbens*

Introduction

Erectile dysfunction (ED), the most common form of sexual dysfunction in sexually active men, is defined as the repeated inability to attain and maintain an adequate erection for satisfactory sexual intercourse. ED results from the loss of penile vascular and smooth muscle relaxation due multiple pathophysiological conditions such hypogonadism, hypertension, type 2 diabetes mellitus (T2D), etc. [1]. Approximately, 90% of T2D men worldwide have been reported to have ED [2]. However, studies have shown that most clinicians do not enquire about sexual dysfunction during medical consultations and the prevalence of self-reported ED is also very low [3, 4].

The pathogenesis through which T2D induces ED result from multiple factors, such as increased formation of advanced glycation end products (AGEs), oxidative stress, deficiency in the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) signaling pathway and hypogonadism [5, 6]. Among these factors, increased formation of AGEs is well-known to form covalent bonds with vascular collagen, causing a vascular thickening, reduced elasticity, endothelial dysfunction, increased vascular stiffness

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were normalized to a loading control (β-Actin) (1:500) (Santa Cruz Biotechnology, Dallas, TX, USA). Chemidoc-XRS imager and image lab version 06 software (Bio-Rad Laboratories, Hercules, CA, USA) was used to Detect and quantify the proteins.

Statistical analysis

Results are presented as the mean ± standard error of the mean (mean ± SEM) in triplicates. Statistical analysis of the differences between mean values obtained from experimental groups were calculated using GraphPad prism (v6.01). Data were subjected to one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. $p \leq 0.05$ was regarded as statistically significant.

Results

Fasting blood glucose (FBG), Mounting frequency and serum testosterone levels

Fasting blood glucose levels, mounting frequency and serum testosterone levels in diabetic induced ED rats after 28 days of treatment are shown in Table 1. The untreated diabetic ED rats presented with persistently higher fasting blood glucose levels. However, a slight decrease in the fasting blood glucose level, when compared to untreated diabetic ED group, was observed in diabetic ED rats treated with the extract for 28 days. Relatively lower testosterone levels, and mounting frequency when compared to the normal group, were also observed in untreated diabetic ED group. However, an increase ($p < 0.001$) in the tested parameters was evident in the animals treated with the extract.

Serum fructosamine, protein thiol group content and uric acid

Figure 2 shows the results of the effect of the extract on serum fructosamine, protein thiol group content and uric acid of the diabetic induced ED rats after 28 days of treatment. Elevated serum levels of fructosamine and lower protein thiol group were observed in the untreated diabetic animals or diabetic animals treated with Cialis, respectively, when compared to the normal control group. However, lower serum levels of the fructosamine content accompanied by a significant increase in protein thiol group concentrations were observed in the diabetic rats treated with the extract or RA-3 when compared to the untreated diabetic animals (Figure 2). Furthermore, a decreased uric acid level was also observed in the diabetic ED group treated with the extract or RA-3 when compared with an increase uric acid level in the untreated diabetic ED group.

Table 1: Effect of extract on FBG, mounting frequency and serum testosterone levels of the experimental rats

Groups	FBG	FBG	Mount frequency	Testosterone (nmol/L)
	Baseline (mmol/L)	Week 21 (mmol/L)	(In 30 mins)	
Normal control	5.27 ± 0.32	5.28 ± 0.05	29 ± 1.02	5.66 ± 0.17
Untreated Diabetic control	12.77 ± 0.56	18.77 ± 0.16	09 ± 1.00	2.23 ± 1.01
Diabetic + Cialis (5mg/kg)	13.13 ± 0.43	15.46 ± 0.08	33 ± 1.01	8.69 ± 2.94
Diabetic + RA-3 (100 mg/kg)	16.37 ± 0.54	7.63 ± 1.52***	31 ± 3.11	8.31 ± 1.57
Diabetic + extract (250 mg/kg)	11.71 ± 0.03	9.11 ± 0.34	42 ± 1.20	10.01 ± 2.58***
ND. Control + extract (250 mg/kg)	5.32 ± 0.01	5.12 ± 0.02	46 ± 1.11	11.93 ± 2.61***

Results are expressed as the mean ± SEM, n = 5. Significantly at ***p<0.001 vs. Diabetic control.

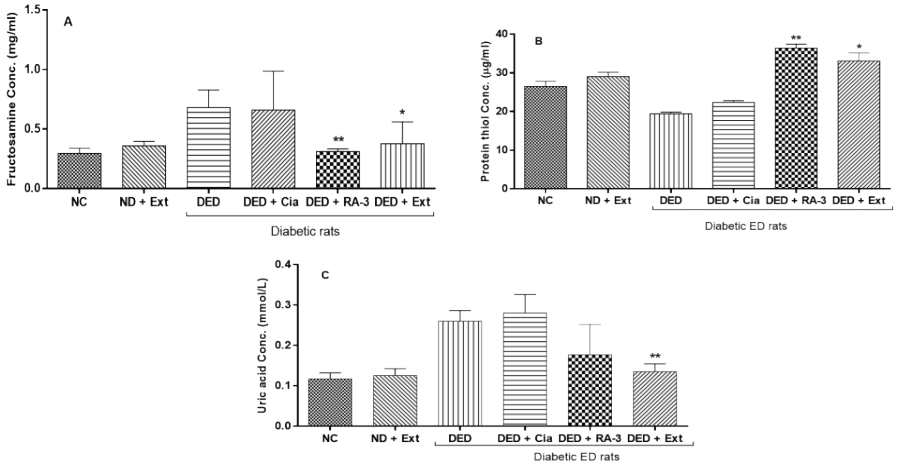

Figure 2: Effect of the methanol extract on fructosamine (A); protein thiol (B) contents and uric acid levels (C). Results are expressed as the mean ± SEM, (n = 5). *p<0.01, ** p<0.001 vs. Untreated diabetic induced ED control. NC – Normal control, ND + Ext – Nondiabetic + extract, DED – diabetic ED control, DED + Cia – Diabetic + Cialis, DED + RA-3 – Diabetic ED + RA-3, DED + Ext – Diabetic ED + extract.

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Effect of the extract on serum antioxidant status

Table 2 shows the results of the effect of the extract on some serum antioxidant levels in the diabetic induced ED rats. Significantly lower SOD and CAT levels along with a relatively higher MDA level were observed in the untreated diabetic ED group animals when compared to the normal control group. However, treatment of the diabetic rats with either extract or RA-3 displayed a significantly ($p \leq 0.001$) increased SOD and CAT levels in comparison to the untreated diabetic-ED animals. This was accompanied by a significant ($p \leq 0.01$) decrease in the MDA levels in extract or RA-3 treated groups.

Effect of the extract on the serum levels of ACE, AChE and arginase

The results of the effect of methanolic roots extract on ACE, AChE and arginase activities are presented in Figure 3. A significantly ($p \leq 0.001$) higher enzyme activities were observed in the untreated diabetic ED rats when compared with the normal control group. However, administration of the extract to the diabetic ED rats for 28 days, significantly ($p \leq 0.001$ and $p \leq 0.0001$) decreased the enzyme activities when compared to the untreated diabetic ED group.

Effect of the extract on the expression of PDE-5, RhoA and eNOS

Effect of the plant extract on the expression of some proteins involved in penile erection process was also investigated. The upregulation of PDE-5 (Figure 4A) and RhoA (Figure 4C) accompanied by down regulated eNOS (Figure 4B) were observed in untreated diabetic ED group when compared to normal rats. A significantly lower expression of PDE-5 and RhoA along with an increased expression of eNOS were observed in the penile tissues of the diabetic induced ED group

Table 2: Effects of methanol extract on serum antioxidants levels of the diabetic animals.

	SOD	CAT	MDA
Groups	**(Inhibition rate %)**	**(mmoles/min/ml)**	**(nmol/µL)**
Normal Control	66.02 ± 1.18	1690.7 ± 295.3	0.03 ± 0.02
Diabetic Control	30.03 ± 2.01	344.0 ± 81.2	0.44 ± 0.04
Diabetic + Cialis (5 mg/kg)	38.88 ± 1.29	650.7 ± 83.3	0.32 ± 0.01
Diabetic + RA-3 (100 mg/kg)	62.08 ± 2.62**	1210.7 ± 88.1***	0.04 ± 0.00***
Diabetic + Extract (250 mg/kg)	65.36 ± 1.18***	1105.3 ± 109.6***	0.09 ± 0.01**
N. Control + Extract (250 mg/kg)	60.82 ± 0.31	1386.67 ± 268.4	0.04 ± 0.01

Results are expressed as the mean ± SEM, n = 5. Significantly at **p<0.01, ***p<0.001 vs. Diabetic control.

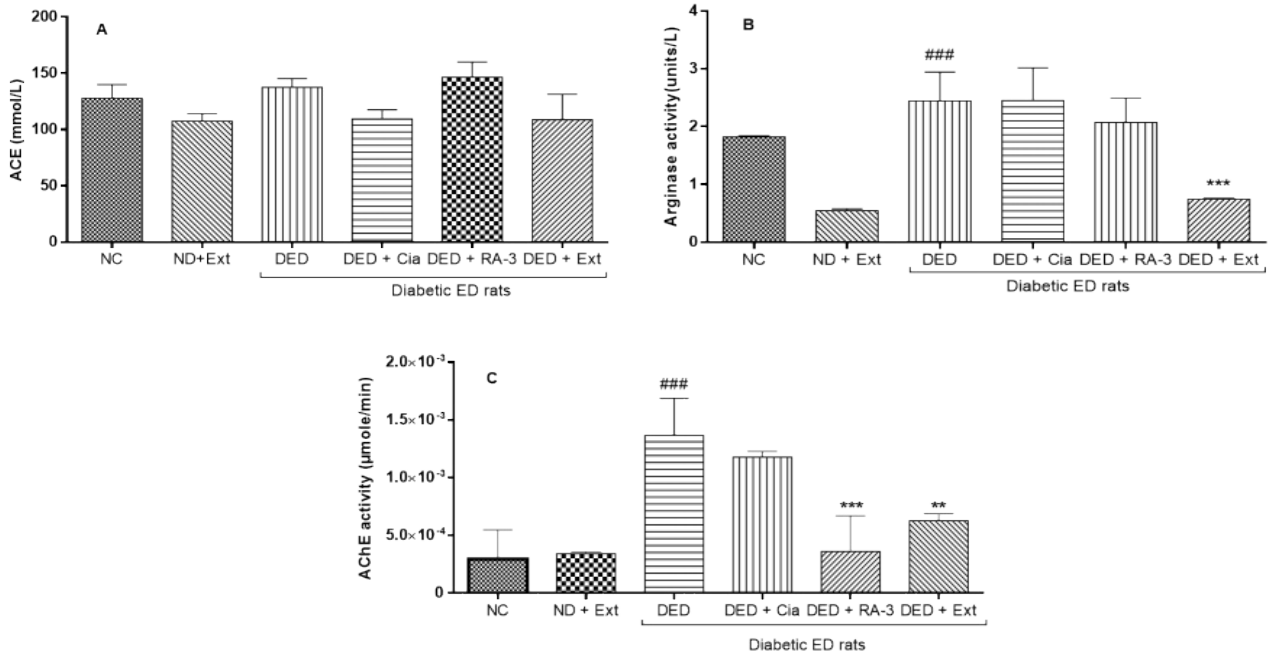

Figure 3: Effect of the methanol extract on ACE (A), arginase (B), and AChE (C) activities. Results are expressed as the mean ± SEM, (n = 5). Significant at ### p<0.001 vs. normal control, *** p<0.0001, and **p<0.001 vs. Untreated diabetic control. NC – Normal control, ND + Ext – Nondiabetic + extract, DED – untreated diabetic ED control, DED + Cia – Diabetic + Cialis, DED + RA-3 – Diabetic ED + RA-3, DED + Ext – Diabetic ED + extract.

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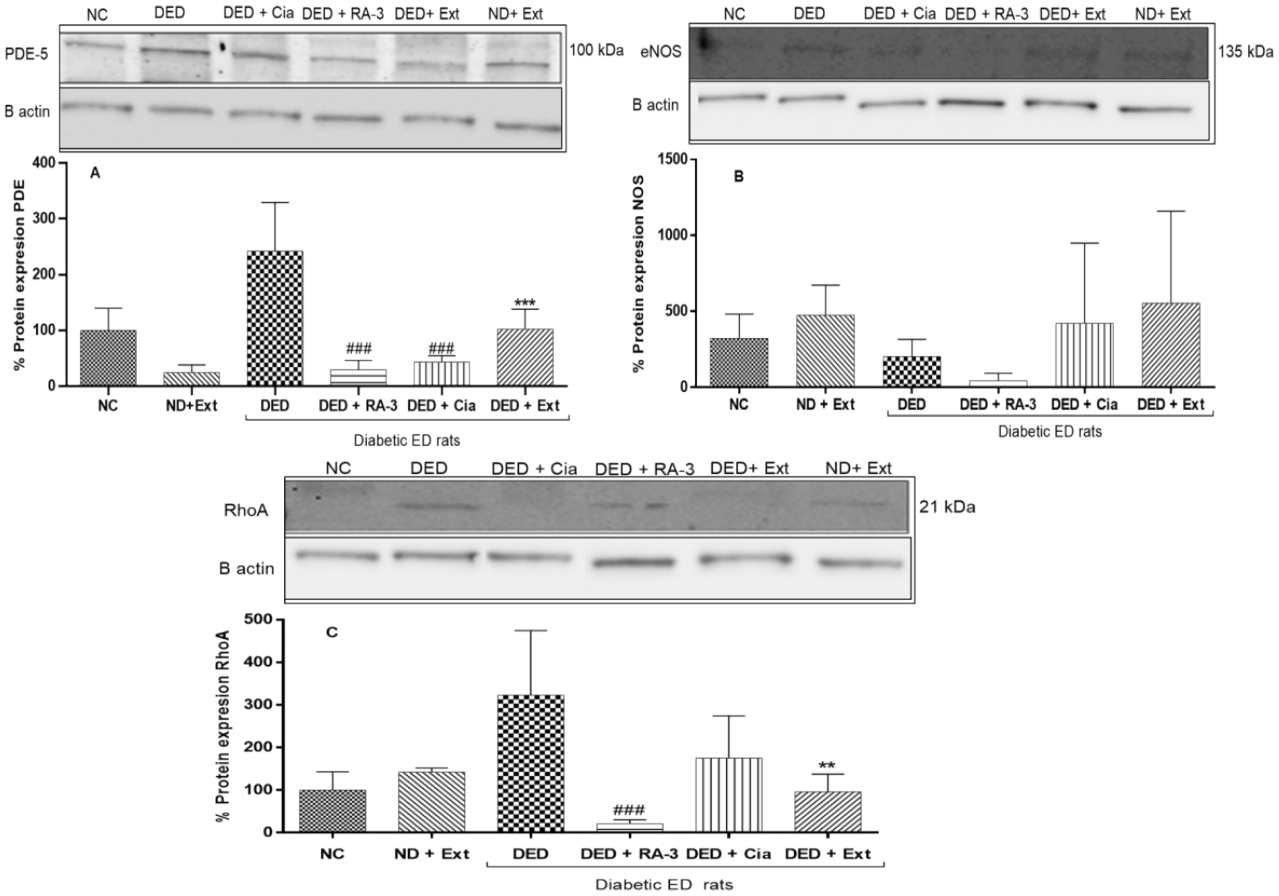

Figure 4: Effect of the methanol extract on PDE-5 (A), eNOS (B) and RhoA (C) expression in type 2 diabetic rats. Values are expressed as the mean ± SD (n=4). ** $p \leq 0.01$ vs. diabetic control, ### $p \leq 0.001$ vs. diabetic control and normal control. NC – Normal control, ND + Ext – Nondiabetic + extract, DED – diabetic control, DED + Cia – Diabetic ED + Cialis, DED + RA-3 – Diabetic + RA-3, DED + Ext – Diabetic + extract.

treated with the extract. Furthermore, a significant decreased expression of PDE-5 and RhoA in the diabetic ED groups treated with RA-3 and Cialis observed was comparable to nondiabetic animals treated with extract.

Discussion

The increasing incidence of type 2 diabetes in men contributes to the increasing number of men with ED [1]. An increasing body of evidence supports the use of medicinal plants in the management of diabetic related complications including ED [20, 21]. In this study, the erectogenic effect of the methanolic extract from the roots of the *M. procumbens* in type 2 diabetic rats is reported.

The recorded elevated fasting blood glucose in the diabetic induced groups confirmed induction of diabetic state in the animals. While mounting behavior characterizes sexual provocation and penile orientation [1], testosterone regulates nearly every component of erectile function. In addition to increasing sexual desire, testosterone also stimulates synthesis of NO, which activates cascade of reactions leading to vasodilation in the penile tissue [22]. In the present study, the reduced mounting frequency and serum testosterone levels in the model diabetic ED rats indicated a decreased sexual desire/libido, a characteristic of ED. The observed increase in mounting frequency and testosterone levels following treatment of the diabetic rats with the extract indicated the erectogenic potential of the extract. In addition, augmented levels of testosterone and increased mounting frequency observed in the normal animals treated with extract further supported its erectogenic boosting ability.

The decreased serum levels of AChE, arginase and ACE in the extract treated groups further supported the erectogenic effect of the plant extract. Increased activities of AChE and arginase, commonly observed in diabetic state, diminishes the synthesis and bioavailability of NO, required for efficient penile erection process [23, 24]. Furthermore, the inhibitory effect of the extract on ACE activity, an enzyme that catalyzes the conversion of the angiotensin I to the active vasoconstrictor angiotensin II [25], indicates a potential to ameliorate hypertension-induced ED. Hence, the control of arginase, AChE and ACE have been reported as potential therapeutic strategy in the management or treatment of ED

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[26]. The enzymatic inhibitory activity exhibited by the extract could be attributed to the phytochemical composition of the plant, which includes saponins, tannins and alkaloids. These phytochemicals are known to inhibit the activities of arginase, AChE, ACE and PDE-5 [27-29].

The ability of the plant extract to lower the serum uric acid levels in the extract treated animals further supported its erectogenic potential. Uric acid, an end product of dietary and endogenous purine metabolism, modulate the physiological functions of various physical systems [30]. However, the link between serum uric acid level and ED is still controversial. Various reports have provided evidence that elevated uric acid level is a powerful scavenger of reactive oxygen species (ROS), thus acts as an antioxidant [31, 32]. Whereas other studies holding the opposite view have revealed that elevated level of uric acid is a potential risk factor of ED [33, 34]. In the current study we found that increased level of uric acid is associated with ED (Figure 2.C), hence, the lowered uric acid level observed on the extract treated rats could partly explain its erectogenic property.

Moreover, understanding the molecular mechanisms that underlie the development and progression of ED is also a vital objective in the management and treatment of the ailment. On one hand, PDE-5 hydrolyses cGMP, a second messenger molecule crucial for activating cascade of reactions leading to vasodilation in the penile tissue [35]. On the other hand, RhoA kinase pathway directly suppress the expression of eNOS, which leads to diminished eNOS activity and reduced bioavailability of NO, thus inhibiting the smooth muscle relaxation and erectile process [36]. The significant downregulation of PDE-5 and RhoA along with an increased expression of eNOS observed in the extract treated group provided support and an insight into the molecular basis of the erectogenic effect of the extract. Our results are similar to those reported by Corbin [24] and Bivalacqua et al [37], who showed the ability of the crude extracts to downregulate RhoA and increase eNOS expression and thus ameliorate erectile dysfunction in diabetic induced ED. Oboh and co-workers [27] have also shown that downregulation of PDE-5 ameliorates erectile dysfunction in diabetic rats .

The ability of the extract to also lower the fasting blood glucose levels (Table 1) and serum fructosamine (Figure 2A), a substance clinically used as a marker of short-term glycemic control in diabetic patients, demonstrated its antihyperglycemic property. The elevated blood glucose levels are known to promote AGEs formation, which accumulate in the corpus cavernosal tissue, particularly in the endothelial and smooth muscle cells, and contribute to the pathogenesis of diabetic ED [38, 39]. AGEs form covalent bonds with vascular collagen, which leads to vascular thickening, reduced elasticity, endothelial dysfunction and increased vascular stiffness [7]. The obtained results from the current work thus show that the crude extract and RA-3 (our in house hyperglycemia control compound [40, 41]) partly possesses a comparable hypoglycemic effect when compared to untreated diabetic ED rats and/or Cialis treated animals, respectively.

Chronic elevated blood glucose also induces oxidative stress which underlies various complications of diabetes including endothelial dysfunction and consequent ED development. Increased activity of SOD and CAT accompanied by decreased MDA levels (a measure of lipid peroxidation) in the extract treated diabetic ED group indicated the extract's potential to enhance antioxidant defense system. The increased protein thiol group content in the extract treated diabetic rats (Figure 2B) further indicated the ability of the extract to enhance endogenous antioxidant status. Protein thiol groups are very vulnerable to oxidation and considered as one of the most valuable body sacrificial antioxidants [42]. The antioxidant property of the extract could play a crucial role in ameliorating diabetic induced erectile dysfunction incidence. Various plants with antioxidant properties have been reported to improve erectile function in diabetic-ED rats [26, 6, 29].

Conclusions

In conclusion, the present study provides evidence that methanolic roots extract of the *Maytenus procumbens* ameliorates diabetic induced erectile dysfunction, suggesting that the plant could potentially be used in the management of diabetic ED. The ameliorative effects of the extract were due to an increased testosterone levels and mount frequency accompanied by inhibitory effect on arginase, ACE and AChE activities in the diabetic ED treated group. In addition, the mechanism through which the extract exerts its erectogenic potential could be attributed to its ability to downregulate PDE-5 and RhoA accompanied by upregulated eNOS. Nevertheless, the effect of the extract on smooth muscle contraction and the histopathological analysis of the penile tissue from the diabetic induced ED in rats is recommended to confirm its erectogenic potential.

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Contribution of authors

NDC analyzed the data; NDC, wrote the manuscript. ARO, RAM and SEM edited the manuscript. All authors read and approved the final manuscript.

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Availability of Data and Materials

All data generated or analyzed during this study are included in this article (however, supporting data are available from the corresponding author on reasonable request).

Conflict of interest: No conflict of interest.

Ethics approval and consent to participate

Approval (Ethical Clearance Number: UZREC 171110–030 PGM 2016/329) for use of laboratory animals (rats) and experimental procedures was granted by the University of Zululand research ethics committee (UZREC).

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