

# Diabetes mellitus-induced male reproductive impairment: The role of natural products: A review

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## ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder characterized by persistent hyperglycaemia, with multi-organ complications. DM is known to trigger oxidative stress in virtually all tissues of the body including male reproductive organs. Several experimental and clinical studies have reported varying degrees of male reproductive impairment in DM. Disruption in the hypothalamic-pituitary-gonadal axis, abnormal testicular energy metabolism, testicular and epididymal oxidative stress and oxidative stress-induced germ cell apoptosis have been reported in DM. The use of natural products in the treatment of various diseases is gaining more attention in experimental and clinical studies for the management and/or treatment of various diseases. In this review, the effects of DM on male reproductive system at pre-testicular, testicular and post-testicular levels are discussed. The role of various natural products including whole plant extracts and some pure compounds isolated from plants, with their suggested mechanism of actions is also reviewed.

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## INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder with a multi-faceted pathogenicity and multi-organ complications. The World Health Organization (WHO) has estimated that the prevalence of DM worldwide will increase to 300 million by 2030 (King, 1999). In 1998, 60 % of the world diabetic population (140 million) was in Asia (King, 1999). Reports from a survey conducted in Malaysia in 1997 showed that over 8 % of the adult population had DM (Zaini, 2000). In a more recent survey, the prevalence of DM among adults in Malaysia was 15.2 % in 2011, and was increased to 17.5 % in 2015 (National Health and Morbidity Survey, 2015).

Until recently, much attention is not given to the effects of DM on reproductive function, since most of the therapeutic interventions are targeted at eliminating the causes of DM and restoring normal health. Nevertheless, it is also important to monitor the effects of the disease on reproductive function. Several complications have been reported following DM, with the implication of oxidative stress (anti-oxidant/oxidant imbalance) as the major factor that is responsible for these complications (La Vignera *et al.*, 2008). This oxidative stress in the reproductive tissues forms the basis of reproductive impairments observed in individuals with DM (Mallidis *et al.*, 2011). DM induces molecular alterations which negatively affect sperm quality and function as well as fertility (Mallidis *et al.*, 2011). La Vignera *et al.*, (2008) in a retrospective study reported the prevalence of subfertility to be 51 % among patients with DM. Another study on infertility among DM patients reported a prevalence of 35.1 % in men with type 2 DM (Bener *et al.*, 2009). Age- dependent erectile dysfunction has also been reported in diabetic males (Young *et al.*, 2004).

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Data from clinical and animal studies have suggested that DM affects male reproductive system at 3 levels namely pre-testicular (Suresh *et al.*, 2012), testicular (Ghosh *et al.*, 2014) and post-testicular levels (Young *et al.*, 2004).

To date, a lot of research has been done to study the role of different natural products in male reproductive functions (Mohamed *et al.*, 2011; Mohamed *et al.*, 2012; Mohamed *et al.*, 2013). Some studies have used whole plant extracts, thus taking advantage of the abundance of different phytochemicals which have several intervention targets, while others have used specific compounds isolated from plants. Several natural products significantly reversed DM-induced reproductive impairment in rats (Ghosh *et al.*, 2014; Khaki *et al.*, 2014). In this review, we emphasize the effects of DM on reproductive function parameters as well as the effects of various natural products on DM-induced reproductive impairment with their possible mechanism(s) of actions.

### CLASSIFICATION OF DIABETES MELLITUS

Diabetes mellitus has been grouped into two main types, namely type 1 DM (T1DM) and type 2 DM (T2DM). T1DM occurs as a result of defective beta cells in the islets of Langerhans. The beta cell abnormality can result from destruction by viral infections, diseases and exposure to various toxic

chemicals (Cooke and Plotnick, 2008). Its classical symptoms are polyphagia, polydipsia, polyuria and weight loss (Cooke and Plotnick, 2008). On the other hand, T2DM is characterized by persistently high blood glucose due to the presence of insulin resistance and usually with relative insulin deficiency. Some of the risk factors for T2DM are genetic predisposition, obesity, hyperlipidemia and history of gestational diabetes. In most cases, the onset of T2DM occurs between the ages of 50-60 years. Following the increasing prevalence of obesity in recent years, there has been a steady increase in the number of younger individuals (some < 20 years old) with T2DM (Kumar *et al.*, 2005).

### EFFECT OF DIABETES MELLITUS ON MALE REPRODUCTIVE FUNCTION

Several animal models of DM have been used in the study of male reproductive function. They include type 1 diabetic rats [streptozotocin (STZ)-induced diabetic rats, alloxan-induced diabetic rats and BioBreeding (BB) rats], type 2 diabetic rats [nicotinamide+STZ-induced diabetic rats (simultaneous administration of nicotinamide and STZ), STZ+high fats diet induced diabetic rats and Goto-Kakizaki (GK) rats]. DM affects male reproductive system at pre-testicular, testicular and post-testicular levels, which are summarized in Figure 1.

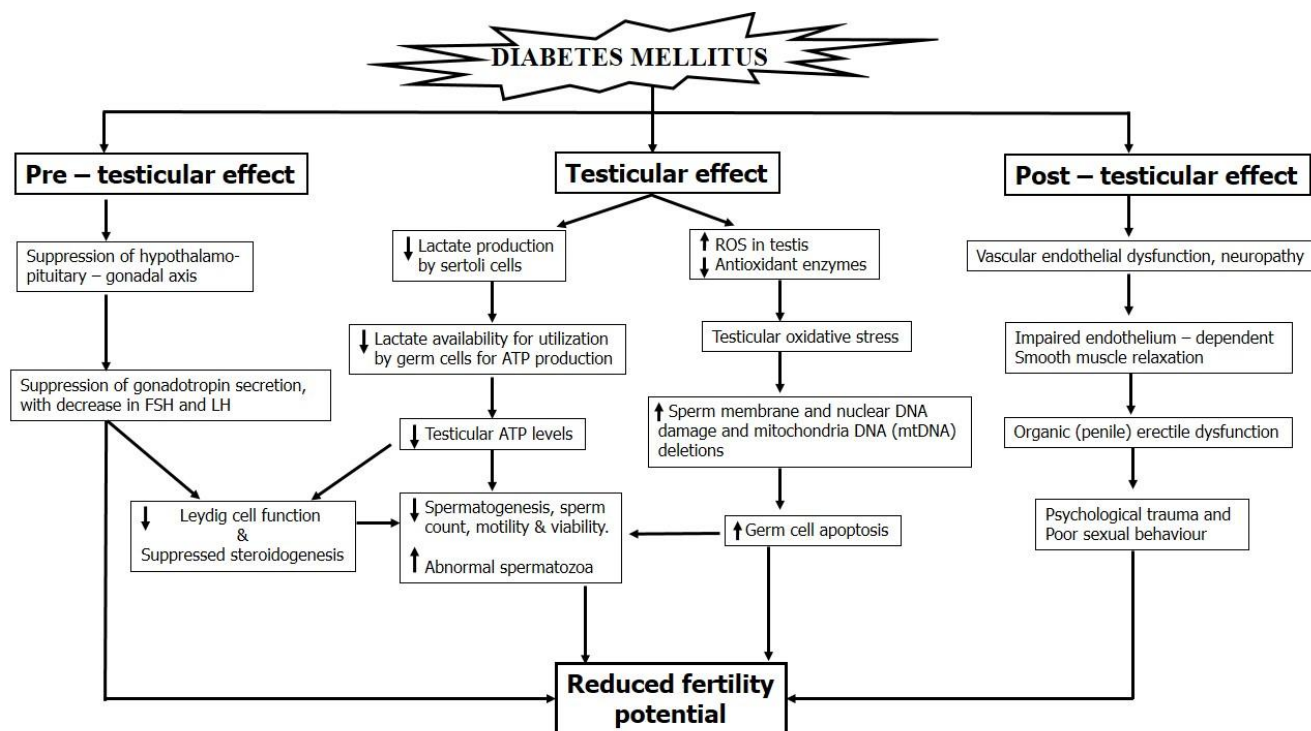


Fig. 1: Summary on the effect of DM on male reproductive system.

### **Pre-testicular effects of diabetes mellitus (hypothalamic-pituitary-gonadal axis)**

Several reports have linked DM with disruption of the hypothalamic–pituitary–gonadal (HPG) axis, thus altering the concentrations of testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH) in males. Baccetti *et al.* (2002) have shown that DM significantly suppresses the HPG axis and lowers FSH and LH responses to exogenous gonadotropin releasing hormone (GnRH) in T1DM patients. Suppressed testosterone secretion as a result of diminished Leydig cell function (Pitteloud *et al.*, 2005) has been reported in T2DM. Decreased serum concentrations of reproductive hormones (testosterone, FSH and LH) have also been reported in DM animal models induced by STZ (Mohasseb *et al.*, 2011; Kanter *et al.*, 2013), alloxan (Hafez, 2010; Ghilissi *et al.*, 2012) and nicotinamide+STZ (Ahangarpour *et al.*, 2015), and in BB rats (Cameron *et al.*, 1990). These studies show a unified pattern of events irrespective of the diabetic model used.

The effect of DM on the HPG axis may not be type specific since the data from both T1 and T2DM models have shown similar findings.

### **Testicular effects**

#### ***Energy metabolism in the testis***

The Sertoli cells (otherwise called nurse cells) are greatly involved in testicular energy metabolism, and form one of the major components of the blood – testis barrier. Testicular energy metabolism shows some form of specificity in which lactate is the main substrate for energy (ATP) production in germ cells (Oliveira *et al.*, 2012). *In vitro* studies with cultured Sertoli cells have shown that removing either insulin (Oliveira *et al.*, 2012) or glucose (Riera *et al.*, 2009) from the culture medium results in adaptation of the Sertoli cells to glucose transport as seen in modulated gene expression of glucose transporters (GLUT1 and GLUT3). However, Oliveira *et al.*, (2012) have reported that the insulin-deprived Sertoli cells in their *in vitro* experiment (which closely mimics T1DM) have reduced glucose utilization even when the gene expression of the glucose transporters is increased. Additionally, the authors have reported down-regulation of the genes associated with lactate metabolism and transport. Recent study by Rato *et al.* (2015) has demonstrated that exposure of cultured Sertoli cells (obtained from T2 diabetic rats) to testosterone increases glucose consumption and up-regulates GLUT3, but down regulates GLUT1 gene expression compared with Sertoli cells culture obtained from pre-diabetic rats. There is also a decrease in protein expression of monocarboxylate transporter-4 (MCT4) and lactate dehydrogenase (LDH), as well as a decrease in LDH activity in Sertoli cell culture obtained from T2 diabetic rats, compared with Sertoli cell culture obtained from pre-diabetic rats (Rato *et al.*, 2015).

*In vivo* studies using STZ-induced T1DM have reported that DM reduces testicular LDH activity (Kyathanahalli and Manjunath, 2014), thus suggesting a likely similar trend of events

in T1 and T2DM. This ultimately implies that the germ cells may be deprived of lactate in diabetic conditions.

#### ***Testicular oxidative stress***

The presence of antioxidants in the testis ensures that the two most important events in the testis namely steroidogenesis and spermatogenesis are not negatively affected by oxidative stress. These antioxidants in the testis are of major significance since oxidative stress is currently regarded as the most important cause of impaired testicular function underlying the pathological consequences of a wide range of conditions including DM. Studies with both T1 and T2 diabetic animal models have shown significant decreases in antioxidant enzymes and a significant increase in lipid peroxidation in the testis. Reports from studies using STZ-induced T1DM rats have shown significant decreases in testicular superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) activities, and a significant increase in malondialdehyde (MDA) level (Mohasseb *et al.*, 2011; Kanter *et al.*, 2013).

In another study using alloxan-induced T1DM rats, Ghilissi *et al.* (2012) have reported significant decreases in the activities of antioxidant enzymes (SOD, CAT and GPx) and a significant increase in thiobarbituric acid-reactive substance level in the testis. A similar trend of results is reported by Hamden *et al.* (2008) using alloxan-induced T1DM rats. On the other hand, Gobbo *et al.* (2015) have reported that DM did not significantly alter the testicular antioxidant defence system as shown by the insignificant alterations in the activities of antioxidant enzymes (SOD, CAT, GPx) and MDA level after 1 week and 8 weeks in STZ-induced T1DM rats.

#### ***Steroidogenesis***

Steroid hormones including testosterone are synthesized from cholesterol through a series of tightly regulated steps. After formation of testosterone, the Leydig cells are involved with its secretion to support spermatogenesis. Studies have reported a significantly increased testicular cholesterol concentration in STZ-induced T1DM model (Saumya and Basha, 2016). Significant decreases in 3 $\beta$ -hydroxysteroid dehydrogenase (HSD) and 17 $\beta$ -HSD activities are found in the testis of STZ-induced T1DM rat model (Reddy *et al.*, 2016). Furthermore, there are significant decreases in expressions of steroidogenic acute regulatory protein (StAR) and cytochrome P450 enzyme (CYP11A1, the first enzymatic step in steroidogenesis) in the testis of STZ-induced T1DM rats.

The increased testicular cholesterol concentration (Saumya and Basha, 2016) may be as a result of down-regulation of the cholesterol transporter, StAR, thus leading to cholesterol accumulation. These results suggest that the reduced serum testosterone concentration in DM amidst high testicular cholesterol concentration may be due to down-regulations of steroidogenic transport protein (StAR) and marker enzymes (CYP11A1, 3 $\beta$ -HSD and 17 $\beta$ -HSD) expressions..

### **Effect of diabetes mellitus on spermatogenesis**

Experimental (Sangameswaran and Jayakar, 2008; Reddy *et al.*, 2016) and clinical (Delfino *et al.*, 2007) evidences have shown that DM negatively affects spermatogenesis and sperm – related parameters. Several studies using STZ-induced T1DM animal model have shown decreased daily sperm production, sperm count and motility (Suresh and Prakash, 2012; Gonzales *et al.*, 2013), and increased percentage of spermatozoa with abnormal morphology (Kanter *et al.*, 2013). Studies using alloxan-induced T1DM animal models (Hafez 2010; Ghilissi *et al.*, 2012) have also yielded similar results.

Reports from clinical studies have failed to completely corroborate those from experimental animals, and most of them have yielded ambiguous results. Vignon *et al.* (1990) have previously reported a significant increase in sperm concentration in T1DM patients, while Garcia-Diez (1991) has reported a significant decrease in sperm count, motility and percentage of spermatozoa with normal morphology. However, Agbaje *et al.* (2007) have found an insignificant increase in sperm concentration and total sperm output with an insignificant decrease in sperm motility, and normal sperm morphology. The authors suggested Leydig cell hyperplasia as the cause of the enhanced spermatogenesis, though with poor motility. These inconsistent findings might be as a result of the lack of information with regards to the duration of exposure to DM and the various control measures adopted by the subjects in each population studied, since most of these studies were conducted using patients reporting to fertility clinics, rather than untreated diabetic volunteers.

### **Testicular histology and germ cell apoptosis in diabetes mellitus**

Oxidative stress, which is one of the hallmarks of DM, has been implicated in DM – induced distorted testicular morphology in diabetic animal models. Studies using T1 (Kanter *et al.*, 2013; Al-Roujeaie *et al.*, 2016) and T2 (Long *et al.*, 2015) diabetic rats have yielded similar results, indicating that testicular histology is negatively affected irrespective of the type of DM. Studies using STZ (Kanter *et al.*, 2013; Al-Roujeaie *et al.*, 2016), alloxan (Shalaby and Hamowieh, 2010; Hafez, 2010) and BB (Cameron *et al.*, 1990) T1DM models have all reported varying degrees of morphological abnormalities, comparable to the study using T2DM (STZ + High fats diet) model (Long *et al.*, 2015). Mean Johnsen's score, a measure of the degree of spermatogenesis, is significantly lower in STZ- induced T1DM model (Kanter *et al.*, 2012; 2013). Testicular atrophy has also been reported in DM with significant decreased volume and diameter of the seminiferous tubule, and decreased numbers of Sertoli and Leydig cells (Kanter *et al.*, 2013; Al-Roujeaie *et al.*, 2016). Kanter *et al.* (2013) have also reported a significantly decreased population of germ cells including spermatogonia, spermatocytes and spermatids at various stages which may explain the decreased testicular weight in DM.

The increased population of apoptotic germ cells observed in diabetic rats is suggestive of the implication of

oxidative stress that usually accompanies DM. Mohasseb *et al.* (2011) have reported an increased activity of the executioner caspase (caspase-3) in the testis of STZ-induced diabetic rats. Up-regulation of the pro-apoptotic protein (Bax) and down-regulation of the anti-apoptotic protein (Bcl-2) have been reported in T1 (Ghosh *et al.*, 2014) and T2 (Long *et al.*, 2015) diabetic rats, with an increase in expression of caspases 8 and 3 (Jiang *et al.*, 2013) in T1 diabetic rats. Zhao *et al.* (2011) have reported up-regulation of the pro-apoptotic genes, p38 and p53 in the testis of STZ-induced T1DM rats. Studies in detecting apoptotic germ cells in the testis of T1 diabetic rats using TUNEL staining technique have reported an increased expression of TUNEL-positive cells (Kanter *et al.*, 2012; 2013).

In the light of the above results, it is clear that all the methods and/or markers used to assess DM- induced germ cell apoptosis show uniformity in the trend of results obtained, thus confirming the increased apoptotic germ cell population in diabetic state.

### **Post-testicular effects of diabetes mellitus (Sexual behaviour and fertility outcome)**

Studies have linked DM with poor sexual urge as a consequence of poor penile erectile function. Studies have shown that DM reduces penile cGMP concentration, prolongs mount, intromission and ejaculatory latencies, and decreases mount and intromission frequencies (Al-Roujeaie *et al.*, 2016). The decreases in sexual behavioural parameters are linked to the reduced Leydig cell secretion of testosterone (Al-Roujeaie *et al.*, 2016). In another study, diabetic male rats have demonstrated subfertility when mated with healthy female rats (Suresh and Prakash, 2012; Reddy *et al.*, 2016).

Reddy *et al.* (2016) have reported an increase in the percentage of pre- and post-implantation losses, and a decrease in the number of live fetuses/dam. DM does not negatively affect pregnancy rate, but prolongs conception time, which is attributed to poor sperm characteristics secondary to DM (Reddy *et al.*, 2016). Taken together, these reports implicate abnormal sexual behaviour in DM- mediated subfertility.

## **NATURAL PRODUCTS AND DM-INDUCED IMPAIRMENT IN MALE REPRODUCTIVE FUNCTION**

Natural products and phytotherapy have been widely embraced lately, probably because of the perceived effectiveness relative to modern medications. This is possibly because of the abundance of various phytochemicals, which have multiple intervention targets in the course of treatment of the targeted condition. Several natural products have been employed in the treatment or management of DM and its accompanying complications. In the subsections below, we also review the role of various natural products [whole extracts (Table 1) and pure compounds isolated from plants (Table 2)] in ameliorating DM-induced male reproductive abnormalities.

**Table 1:** Selected studies reporting the effect of natural products on DM – induced reproductive impairment.

Diabetic Model	Type of DM	Natural product (part used)	Dose (duration of treatment)	Anti-diabetic Standard	Effect on FBG	Outcome on Reproductive function parameters
STZ-induced DM	T1DM	<i>Amaranthus spinosus</i> (stem)	250 and 500mg/kg/day, (15 days)	Glibenclamide	↓#	↑ Testicular weight, testosterone, spermatogenesis (Sangameswaran and Jayakar 2008).
		Brazilian propolis	100mg/kg/day, (8 weeks)	Glucobay	↓#	Not investigated (Zhu <i>et al.</i> , 2011).
		Chinese propolis	100mg/kg/day, (8 weeks)	Glucobay	↓#	Not investigated (Zhu <i>et al.</i> , 2011).
		<i>Chlorophytum borivilianum</i> (root)	200mg/kg/day, (28 days)	Glibenclamide	↓#	↑ Sperm count, motility, viability and % normal morphology; ↓ oxidative stress and apoptosis in sperm (Thakur <i>et al.</i> , 2009).
		<i>Chlorophytum borivilianum</i> (root)	200mg/kg/day, (28 days)	–	↓#	↑ Sexual behaviour (Thakur <i>et al.</i> , 2009).
		<i>Chlorophytum borivilianum</i> (tuber)	100 and 300mg/kg/day, (14 days)	–	–	↑ Sexual behaviour (Vyawahare <i>et al.</i> , 2009).
		<i>Cinnamon zeylanicum</i>	75mg/kg/day, (8 weeks)	–	↓	↑ Serum testosterone, sperm count, motility and viability (Khaki <i>et al.</i> , 2014).
		<i>Curculigo orchioides</i>	100 and 200mg/kg/day, (28 days)	Glibenclamide	↓#	↑ Serum testosterone, sperm count; improved sexual behaviour and penile erection index (Thakur <i>et al.</i> , 2012).
		<i>Danae racemosa</i> (leaves)	400mg/kg/day, (28 days)	–	–	↑ Serum testosterone, testis weight (Shahreari <i>et al.</i> , 2010).
		<i>Dracaena arborea</i> (root bark)	100 and 500mg/kg/day, (4 weeks)	–	↓	↑ Sexual behaviour (Wankeu-Nya <i>et al.</i> , 2014).
		<i>Dracaena arborea</i> (root bark)	100 and 500mg/kg/day, (3 weeks)	–	↓	Improved erectile function (Wankeu-Nya <i>et al.</i> , 2013).
		<i>Eugenia jambolana</i> (seeds)	200mg/kg, twice daily, (60 days)	–	–	↑ Serum testosterone, testis weight and sperm count; ↓ Bax and ↑ Bcl-2 expression in the testis; ↑ germ cell regeneration (Ghosh <i>et al.</i> , 2014).
		<i>Hibiscus sabdariffa</i> (calyx)	100mg/kg/day, (28 days)	–	↓#	↑ Testicular weight, sperm count, motility; ↓ abnormal morphology (Idris <i>et al.</i> , 2012).
		<i>Ligustrum lucidum</i> (fruit)	30g/kg/day, (110 days)	–	–	↑ Serum testosterone, FSH and LH (Feng <i>et al.</i> , 2001).
		<i>Mucuna pruriens</i> (seeds)	200mg/kg/day, (60 days)	–	↓#	↑ Serum testosterone, FSH, LH; ↑ weight of testis, epididymis, prostrate and seminal vesicle; ↑ DSP, sperm count, motility and viability; ↑ erectile function and sexual behaviour (Suresh and Prakash 2012).
		<i>Musa paradisiaca</i> (root)	200mg/kg twice daily, (28 days)	Glibenclamide	↓#	↑ Serum testosterone; ↓ testicular cholesterol; ↑ sperm count, motility; improved testicular, epididymal and sperm antioxidant status; decreased testicular germ cell apoptosis; improved testicular histology (Chatterjee <i>et al.</i> , 2012).
		<i>Musa paradisiaca</i> (root) + <i>Coccinia indica</i> (leaves)	20mg/kg/day, (45 days)	–	↓#	↑ Serum testosterone; ↑ sperm count and viability; ↓ testicular oxidative stress and germ cell apoptosis (Mallick <i>et al.</i> , 2010).
		<i>Parkia biglobosa</i> (seeds)	200 and 400mg/kg/day, (28 days)	Insulin	–	↑ Serum testosterone; improved testicular antioxidant (Ogunyinka <i>et al.</i> , 2016).
		Sesame oil	5 and 10% diet (56 days)	–	↑	↑ Serum testosterone, sperm motility and viability; ↓ abnormal morphology (Abbasi <i>et al.</i> , 2013).
		<i>Spirulina maxima</i> (pellets)	200mg/kg/day, (4 weeks)	–	↓	↑ Testis weight, testosterone, Leydig cell density, steroidogenesis (Nah <i>et al.</i> , 2012).
<i>Withania somnifera</i> (roots)	500mg/kg/day, (15 days)	–	↓#	↑ Testis weight, antioxidant enzymes and ↓ lipid peroxidation; ↑ testicular LDH and 3β-HSD (Kyathanahalli and Manjunath 2014).		
<i>Zingiber officinale</i> (root)	100mg/kg/day, (8 weeks)	–	↓	↑ Serum testosterone, sperm count, motility and viability (Khaki <i>et al.</i> , 2014).		

Alloxan – induced DM	T1DM	<i>Chlorophytum borivilianum</i> (root)	100 and 300mg/kg/day, (28 days)	–	↓#	↑ Sexual behaviour (Vyawahare <i>et al.</i> , 2009).
		<i>Nigella sativa</i> (seeds)	2% in diet (30 days)	–	↓#	↑ Weight of testis, epididymis, seminal vesicle and prostate; ↑ serum testosterone, sperm count and motility; ↓ testicular LDH and oxidative stress (Ghissi <i>et al.</i> , 2012).
		<i>Zingiber officinale</i> (root)	100 and 200mg/kg/day, (65 days)	–	↓	↑ Serum testosterone, testis weight, sperm count, sperm motility; ↓ testicular lesions, ↑ fertility index (Shalaby and Hamowieh 2010).
		<i>Zingiber officinale</i> (root)	250 and 500mg/kg/day, (65 days)	–	↓	↑ Weight of testis, seminal vesicle and prostate; ↑ sperm count, motility, viability and ↓ abnormality (Hafez 2010).
Nicotinamide + STZ – induced DM	T2DM	<i>Arctium lappa</i> (root)	200 and 300mg/kg/day, (28 days)	Glibenclamide	–	↑ Sperm viability (Ahangarpour <i>et al.</i> , 2015).
		<i>Rhus coriaria</i> (seeds)	200 and 400mg/kg/day, (28 days)	Glibenclamide	–	↑ Serum testosterone, FSH, LH, testis weight, sperm count, viability (Ahangarpour <i>et al.</i> , 2014).

All treatments are given orally; # represents a significant decrease in fasting blood glucose (FBG) level compared with the diabetic control group.

**Table 2:** Selected studies reporting effects of pure compounds isolated from plants on DM-induced reproductive impairment.

Diabetic Model	Type of DM	Compound (class of compound)	Dose (duration of treatment)	Anti-diabetic Standard	Effect on FBG	Outcome on Reproductive function parameters
STZ-induced DM	T1DM	Curcumin (phenol)	100mg/kg/day, (8 weeks)	–	↓	↑ Testicular weight, serum testosterone; ↓ testicular oxidative stress; improved testicular cytoarchitecture and ↓ germ cell apoptosis (Kanter <i>et al.</i> , 2013).
		Naringenin (flavanone)	5 and 10mg/kg/day, (10 weeks)	–	↓#	↑ Serum testosterone, sperm count, motility, viability; improve spermatogenesis; increase Sertoli cell number; ↓ testicular oxidative stress; ↓ testicular inflammation and apoptosis (Roy <i>et al.</i> , 2013).
		Quercetin (flavonoid)	15mg/kg/day, <i>ip</i> (4 weeks)	–	–	↑ Sperm count, motility and viability; ↓ sperm oxidative stress (Khaki <i>et al.</i> , 2009).
		Quercetin (flavonoid)	15mg/kg/day, <i>ip</i> (4 weeks)	–	↓	↑ Testicular weight, serum testosterone, sperm count, motility and viability; improved testicular cytoarchitecture (Khaki <i>et al.</i> , 2010).
		Quercetin (flavonoid)	15mg/kg/day, <i>ip</i> (8 weeks)	–	–	↑ Testicular weight, serum testosterone; ↓ testicular glucose and oxidative stress, improved testicular cytoarchitecture and ↓ germ cell apoptosis (Kanter <i>et al.</i> , 2012).
		Resveratrol (phenol)	5mg/kg/day, (8 weeks)	–	↑	↓ Oxidative stress in corpus cavernosum, ↓ corporal tissue apoptosis and ↑ penile erectile function (Yu <i>et al.</i> , 2013).
		Rutin (flavonoid)	50 and 100mg/kg/day, (5 weeks)	–	↓	↑ Testicular weight and serum testosterone; ↓ testicular oxidative stress; improved sexual behaviour; improved testicular cytoarchitecture (Al-Roujeaie <i>et al.</i> , 2016).
STZ + High fats diet – induced DM	T2DM	Scutellarin (phenol)	100mg/kg/day, (60 days)	–	↓	↑ Testicular and epididymal weights, ↑ testicular microcirculation, ↓ testicular oxidative stress, improved testicular cytoarchitecture and ↓ germ cell apoptosis (Long <i>et al.</i> , 2015).

All treatments are given orally except for the studies using quercetin; *ip* = intraperitoneally. # Represent a significant decrease in fasting blood glucose (FBG) level compared with the diabetic control group.

### Natural products with pre-testicular (HPG-axis) beneficial effects in diabetes mellitus

Investigations using T1 diabetic rats have shown that administration of fruit extract of *Ligustrum lucidum* (Feng *et al.*, 2001) or seed extract of *Mucuna pruriens* (Suresh and Prakash, 2012) for 60 days significantly increases serum concentrations of testosterone, FSH and LH. Seed extract of *Rhus coriaria* has been

demonstrated to have a similar effect in T2 diabetic rats (Ahangarpour *et al.*, 2015). All other plant extracts have been reported to have an effect on the HPG-axis but only limited their findings to testosterone concentration (Table 1). Studies using pure compounds of plant origin (Table 2) have also been reported to improve testosterone concentration in T1 and T2 diabetic animal models. Curcumin, a phenol, has been shown to increase serum

testosterone concentration in T1 diabetic rats after 8 weeks of treatment (Kanter *et al.*, 2013). Flavonoids like quercetin (Khaki *et al.*, 2010; Kanter *et al.*, 2012) and rutin (Al-Roujeaie *et al.*, 2016) are reported to also improve serum testosterone concentration in T1 diabetic rats. Similarly, flavanone naringenin is shown to increase serum testosterone concentration in T1 diabetic rats after 10 weeks of administration (Roy *et al.*, 2013). It is suggested that an increase in testosterone secretion helps in normal spermatogenesis for the production of normal and healthy spermatozoa.

#### Natural products with testicular effects in diabetes mellitus

The effects of DM on the testis seem to revolve around abnormal glucose metabolism in the testis and reduced availability of ATP for the two key events (steroidogenesis and spermatogenesis) in the testis. However, most of the studies on natural products do not show sufficient data on testicular energy metabolism in diabetic animal models. Only a few studies have reported their effects on LDH. Arikawe *et al.* (2012) have reported that administration of *Zingiber officinale* extract to STZ-induced T1 diabetic rats reverses the increased LDH activity in the testis. Kyathanahalli and Manjunath (2014) have also reported a similar finding after 15 days administration of the root extract of *Withania somnifera*. In a study using flavonoid quercetin, Kanter *et al.* (2012) have reported a reduced concentration of glucose in the testis homogenate of STZ-induced T1 diabetic rats after quercetin supplementation. This suggests that quercetin controls testicular hyperglycaemia. However, testicular glucose is the only testicular energy metabolism-related parameter assessed in this study thus making it difficult to suggest the mechanism of action. Some authors have suggested that an increase in tissue LDH activity is characteristic of tissue damage associated with exposure to xenobiotics (Srivastava and Pant, 2003). Therefore, assessment of LDH activity alone is not sufficient to demonstrate the effects of natural products on testicular glucose regulation.

A study on T1DM using *Musa paradisiaca* root extract has demonstrated decreased cholesterol level and increased testosterone in the testis of diabetic rats after 28 days of administration (Chatterjee *et al.*, 2012). Increased expressions of StAR and 17 $\beta$ -HSD, with no significant effect on 3 $\beta$ -HSD, in addition to increased serum testosterone concentration are found in T1 diabetic rats treated with *Spirulina maxima* for 4 weeks. It is suggested that with the increased StAR protein expression compared to the DM group, more cholesterol would be delivered to the mitochondria of Leydig cells for testosterone synthesis (Nah *et al.*, 2012). Kyathanahalli and Manjunath (2014) have reported an increase in expression of 3 $\beta$ -HSD in T1 diabetic rats following 15 days administration of *Withania somnifera*. Nevertheless, studies using other plant extracts have no reports showing their effects on the markers of steroidogenesis, even though some have reported an improved serum concentration of testosterone (Table 1). Spermatogenesis is negatively affected when steroidogenesis is suppressed, as observed in DM. Studies using whole plant extracts

(Mallick *et al.*, 2010; Hafez 2010; Gonzales *et al.*, 2013) and compounds of plant origin (Khaki *et al.*, 2009; Khaki *et al.*, 2010; Roy *et al.*, 2013) have shown a significant improvement in spermatogenesis, in which sperm count, normal morphology, viability and motility are significantly increased (Tables 1 and 2). Furthermore, curcumin (Kanter *et al.*, 2013) and quercetin (Kanter *et al.*, 2012) have improved spermatogenesis, as shown by an increase in mean testicular biopsy score after 8 weeks of treatment. Several studies have demonstrated the beneficial effects of plant-based products on DM-induced oxidative stress in the sperm and testis of rats. Studies have shown that administration of root extract of *Chlorophytum borivillianum* for 28 days reduces nitric oxide, hydrogen peroxide and MDA levels in the sperm of STZ-induced T1 diabetic rats (Thakur *et al.*, 2009). Khaki *et al.* (2009) have demonstrated that quercetin decreases MDA concentration and increases total antioxidant capacity of sperm in STZ-induced T1 diabetic rats. Studies using other plant extracts have yielded similar results in the testicular tissue. For example, the combined root extract of *Musa paradisiaca* and leave extract of *Coccinia indica* improves antioxidant enzymes activities and reduces lipid peroxidation in the testis of T1 diabetic rats after 45 days of administration (Mallick *et al.*, 2010).

Testicular germ cell apoptosis is reported to be lower in diabetic rats treated with *Musa paradisiaca* + *Coccinia indica* (Mallick *et al.*, 2010) and *Eugenia jambolana* (Ghosh *et al.*, 2014). Similarly, Thakur *et al.* (2009) have reported a decrease in apoptosis of spermatozoa of T1 diabetic rats following 28 days administration of *Chlorophytum borivillianum* root extract. In addition, the activity of caspase-3 in the spermatozoa is significantly decreased compared to the diabetic untreated rats (Thakur *et al.*, 2009). Studies using phenolic compounds have also yielded a similar trend of results. Administration of curcumin (Kanter *et al.*, 2013) or quercetin (Kanter *et al.*, 2012) for 8 weeks decreases apoptotic index in the testis of T1 diabetic rats. Administration of scutellarin for 60 days down-regulates Bax protein and up-regulates Bcl-2 in T2 diabetic rats (Long *et al.*, 2015). Administration of naringenin significantly decreases the number of TUNEL-positive cells in the testis (Roy *et al.*, 2013), implying a decrease in testicular germ cell apoptosis.

#### Natural products with post-testicular beneficial effects in diabetes mellitus

Natural products have demonstrated significant beneficial effects in treating impaired sexual behaviour associated with DM (Tables 1 and 2). For example, *Dracaena arborea* root bark and *Mucuna pruriens* seeds extract significantly improve erectile function in T1 diabetic rats after 3 weeks and 40 days of treatment, respectively, compared to the DM untreated rats (Suresh and Prakash, 2012; Wankeu-Nya *et al.*, 2014). Similarly, flavonoid rutin increases cGMP concentration in the homogenate of the penile tissue of T1 diabetic rats after 5 weeks of treatment (Al-Roujeaie *et al.*, 2016). The root extract of *Chlorophytum borivillianum* decreases mount, intromission and ejaculation

latencies, and increases their frequencies in T1 diabetic animal models (Thakur *et al.*, 2009; Vyawahare *et al.*, 2009). Wankeu-Nya *et al.* (2014) have reported significant decreases in mount, intromission and ejaculatory latencies after 4 weeks of treatment of T1 diabetic rats with root bark extract of *Dracaena arborea*. *Curculigo orchoides* extract significantly decreases mount, intromission and ejaculatory latencies and frequencies in T1 diabetes, (Thakur *et al.*, 2012). Similarly, rutin significantly reduces mount, intromission and ejaculatory latencies, and increases their frequencies (Al-Roujeaie *et al.*, 2016). These results may suggest that natural products can ameliorate DM-induced impaired sexual behaviour and erectile dysfunction. Nevertheless, further studies are suggested to be carried out using these natural products to elucidate their mechanism of actions.

## NATURAL PRODUCTS AND BLOOD GLUCOSE REGULATION IN DIABETES MELLITUS

A greater percentage of the natural products examined in this review significantly reduces fasting blood glucose of diabetic rats as compared to their diabetic untreated counterparts (Table 1). This observation is in addition to their significant beneficial effects on male reproductive function. Several studies have shown that natural products cause pancreatic  $\beta$ -cells regeneration and improve the secretion and viability of insulin (Giribabu *et al.*, 2014; Koneri *et al.*, 2014). Additionally, natural products by virtue of the fact that most of them contain flavonoids and phenolic compounds, have antioxidant property to reduce the oxidative stress associated with DM (Giribabu *et al.*, 2014; Ogunyinka *et al.*, 2016).

## CONCLUSION AND FUTURE DIRECTION

In conclusion, the studies discussed in this review have suggested a beneficial effect of natural products on DM-induced reproductive abnormalities at the pre-testicular, testicular and post-testicular levels. However, it is suggested to also include studies on their phytochemical compounds, toxicity as well as standard anti-diabetic agent(s) as positive controls to better appreciate their potential to attenuate DM-induced impairment in reproductive function.

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