Modulation of diabetes-mellitus-induced male reproductive dysfunctions in experimental animal models with medicinal plants

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ABSTRACT

Today diabetes mellitus has emerged as a major healthcare problem throughout the world. It has recently broken the age barrier and has been diagnosed in younger people also. Sustained hyperglycemia is associated with many complications including male reproductive dysfunctions and infertility. Numerous medicinal plants have been used for the management of the diabetes mellitus in various traditional system of medicine and in folklore worldwide as they are a rich source of bioactive phytoconstituents, which lower blood glucose level and/or also act as antioxidants resulting in the amelioration of oxidative-stress-induced diabetic complications. The present review describes the ameliorative effects of medicinal plants or their products, especially on male reproductive dysfunctions, in experimental diabetic animal models.

Key words: Antioxidant, blood glucose, sperm function, testosterone, testis

INTRODUCTION

Diabetes mellitus (DM) is a chronic, complicated metabolic disorder characterized by hyperglycemia, which often results from defects in insulin secretion, insulin action, or both. Moreover, DM is associated with severe disturbances of carbohydrate, fat, and protein metabolism.[1]

Diabetes is rapidly emerging as a major public health challenge and demands special attention towards its management. According to the diabetic atlas of the International Diabetic Federation, 366 million people were affected by diabetes worldwide in 2011, and diabetes prevalence is expected to 522 million by 2030.[2] Furthermore, the increasing prevalence of diabetes mellitus in children and adolescents is also of concern. Poorly managed diabetes can lead to a large number of complications including retinopathy, neuropathy, nephropathy, cardiovascular diseases, and male impotency.[3,4]

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A large number of studies, both in diabetic men and animal models indicate that DM causes male infertility based on impotency, retrograde ejaculation, and hypogonadism. DM may affect male reproductive functions at multiple levels including variation in sperm quality, altered spermatogenesis, morphological changes in testes, altered glucose metabolism in Sertoli-blood testes barrier, reduced testosterone, ejaculatory dysfunction, and reduced libido.[5-13] Several clinical and animal studies have focused on the molecular mechanism responsible for the alterations induced by DM in male reproductive potential including endocrine disorders, neuropathy, and increased oxidative stress.[12]

DM-induced adverse effects on male reproductive functions might be mediated through hormonal alterations in the hypothalamic-pituitary-gonadal axis or through the direct interactions of insulin with the testes and sperm cells, as both the testes and sperms themselves produce insulin.[11] Insulin expression in the testes also seems to be affected by diabetes.[14] Both diabetic men and knockout mice had notably impaired spermatogenesis, increased germ cell depletion, and Sertoli cell vacuolization, suggesting that insulin may have an important role in spermatogenesis.[6,15] It is still unclear whether the effects of diabetes on male fertility are mediated through testicular insulin insufficiency or through systemic effects of diabetes.[16-18]

Furthermore, oxidative stress may play a pathogenic role in diabetes-related male reproductive function abnormalities.[12] Studies have shown that men suffering from diabetes have sperms with greater DNA fragmentation and an increase in

Table 1: Review of the literature of various plants/herbs showing modulatory effect on reproductive dysfunctions in male diabetic animals

Plant (family)	Part used	Extract	Dose/mode/duration	Animal models	Effect on blood glucose, insulin	Effects observed on reproductive functions	References
Allium ascalonicum (Liliaceae)	Bulb	Juice	0.5 and 1.0 g/100 g b. wt./day, orally for 14 days	STZ-induced diabetic mice	Decrease in the blood glucose level	Attenuated the diabetes induced impaired testicular functions including the increase of gonadal index, sperms count, motile and viable sperms and a decline in the number of abnormal sperms. The effects might due to antioxidant quercetin, a major component of red onion, which exhibited protective effects on testicular damage induced by oxidative stress	Luangpirom *et al.*[27]
Allium cepa (Liliaceae)	Bulb	Juice	1 ml/day/rat by gavage for 4 weeks	STZ-induced diabetic rats	-	Significantly increased epididymal sperm count, percentage of viabile and motile sperms, serum total testosterone level and reduced the level of ROS in serum as compared to diabetic control. The result indicate that these preventive effect might be due to decrease in ROS	Gholamhosimi *et al*[28]
Allium sativum (Liliaceae)	Bulb	Juice	1 ml/100 g b.wt./day by gavage for 6 weeks	STZ-induced diabetic rats	Significant lowering of blood glucose level	A significant increase in the number of Leydig cells, testis weight, serum levels of testosterone and estradiol was noticed. These effects suggest that the juice supplementation could play both preventive and therapeutic role	Abdolahnejad *et al.*[29]
Amaranthus spinosus (Amaranthaceae)	Stem	Methanolic extract	250 and 500 mg/kg b.wt./day, orally for 15 days	STZ-induced diabetic rat	Significant decline in the blood glucose level	Caused a significant increase in the weight of testis sperm count, levels of testosterone in both serum and testes as compared to diabetic control rats	Sangameswaran and Jayakar[30]
Asparagus racemosus (Liliaceae)	Root	Aqueous extract	-	STZ/ALX-induced diabetic rats	-	Ameliorated the mounting, ejaculation and intromission latencies as well as frequencies, hesitation time and copulatory rate in diabetic rats. These results support aphrodisiac nature of the herb for treating sexual dysfunctions in diabetic rats	Thakur *et al.*[31]
Camellia sinensis (Theaceae)	Leaves	Aqueous extract	10 g/750 ml deionized boiled water for 30 days	ALX-induced diabetic rats	-	There was a significant increase in the weights of epididymis and seminal vesicles and in the number of live sperms with significant decrease in prostate gland weight, abnormal and dead sperm numbers. The histoarchitecture of testis also improved in extract treated diabetic control rats. These modulatory changes may be due to antioxidant effect of extract	Jassem *et al.*[32]
Chlorophytum borivilianum (Liliaceae)	Tuber	Hydro-alcoholic extract	100 and 300 mg/kg b.wt./day, orally for 14 days	STZ-induced diabetic rats	-	A significant decrease in the mount latency in addition with intromission, ejaculation latencies and the post ejaculatory interval was observed. The extract treatment also enhanced the sexual vigor and hit rate in the diabetic rats. The reduction in oxidative stress associated with free radicals and ROS could be its probable mechanism in alleviating impotency in diabetec rats	Vyawahare *et al.*[33]

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Table 1: Contd...

Plant (family)	Part used	Extract	Dose/mode/duration	Animal models	Effect on blood glucose, insulin	Effects observed on reproductive functions	References
Cinnamon zeylanicum (Lauraceae)	Bark	Ethanolic extract	250 and 500 mg/kg b.wt./day, orally for 65 days	ALX-induced diabetic rats	Significantly decreased serum glucose level	A significant increase in the sperm progressive motility, sperm count, viability and serum testosterone level was noticed in extract treated diabetic rats. Histological picture of testes revealed normal structure of seminiferous tubules. The effects may be due to antidiabetic and antioxidant activity of the extract	Hafez[34]
Citrullus vulgaris (Curcurbitaceae)	Seeds	70% Methanolic extract	55 mg/kg b.wt./day, orally for 4 weeks	STZ-induced diabetic rats	Significant decrease in blood glucose level	Significantly increased the epididymal sperm count, serum testosterone and TAC levels. These effects might be due to antidiabetic, antioxidant activity of the phytoconstituents present in the extract	Khaki *et al*.[35]
Cnidoscolus aconitifolius (Euphorbiaceae)	Leaves	Ethanolic extract	100, 500 and 1000 mg/kg b.wt./day, orally for 4 weeks	ALX-induced diabetic rats	-	Significantly improved caudal epididymal sperm count, motility and live/dead ratio but no effect on sperm structural abnormalities	Azeez *et al*.[36]
Cocculus hirsutu (Menispermaceae)	Aerial part	Methanolic extract	400 and 800 mg/kg b.wt./day for 15 days	STZ-induced diabetic rats	Significant decrease in the blood glucose level and an increase in insulin secretion	Significantly increased the weight of reproductive organs and cauda epididymal sperm count, motility and testosterone level in both testes and serum. Resumption of spermatogenesis in seminiferous tubules was also observed. These effects may be due to the insulogenic and androgenic activity of the extract	Sangameswaran and Jayakar[37]
Curculigo orchioides (Amaryllidaceae)	Rhizome	Aqueous extract	100 and 200 mg/kg b.wt./day, orally for 28 days	STZ-induced diabetic wistar rats	Significant decrease in blood glucose level	Significantly increased serum levels of testosterone and the weight of testes and prostate. Ameliorated the male sexul behavior, sperm count, penile erection index, seminal fructose content, antioxidants and anabolic activities. The effects might be due to the presence of steroids and steroidal saponins in the extract which exerts antioxidant and anabolic activity	Thakur *et al*.[38]
Danae racemosa (Ruscaceae)	-	Aqueous extract	400 mg/kg b.wt./day, orally for 28 days	STZ-induced diabetic rats	-	An increase in serum testosterone and the testes weight was observed as compared to diabetic control rats. This might be due to reduced production of ROS in extract treated diabetic rats	Shahreari *et al*.[39]
Dracaena arborea (Asparagaceae)	Root bark	Ethanolic and aqueous extract	100 and 500 mg/kg b.wt./day, orally for 3 weeks	STZ-induced diabetic rats	No significant change in blood glucose level	Significantly improved testis morphology and reversed the impairment of spermatogenesis in diabetic rats. This may be due to antioxidant and androgenic effects of flavonoids, phenols, saponins and phytosterols present in the extract	Wankeu-Nya *et al*.[40]
Eugenia jambolana (Myrtaceae)	Seeds	Hydro-methanolic (40:60) extract	20 mg/100 kg b.wt./twice a day, orally for 60 days	STZ-induced diabetic rats	Significant recovery in the level of glycated haemoglobin.	A significant recovery in the weight of reproductive organs, epididymal sperm count, serum level of testosterone and expression of Bax and Bcl-2 gene in testicular tissue was observed. This may be due to antioxidant, antidiabetic and antiapoptotic effects of the extract which leads to improvement of testosterone biosynthesis	Ghosh *et al*.[41]
Ficus deltoidea (Moraceae)	Leaves	Aqueous and Ethanolic extract	800 mg/kg b.wt./day, orally for 4 weeks.	ALX-induced diabetic rats	Significant decrease in blood glucose level	Significant improvement in the sperm count, sperm motility, LDH-C4 activity and testosterone concentration along with reduction in sperm abnormalities was noticed	Awang *et al*.[42]

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Plant (family)	Part used	Extract	Dose/mode/duration	Animal models	Effect on blood glucose, insulin	Effects observed on reproductive functions	References
Hibiscus sabdariffa (Malvaceae)	Calyx	Aqueous extract	100 mg/kg b.wt./day, orally for 28 days	STZ-induced diabetic rats	Significantly lowered the fasting blood glucose level and increased plasma insulin level	Significantly increased reproductive organ weights, epididymal sperm count, sperm motility and plasma level of FSH and reduced sperm abnormalities. The protective effects of extract might be due to its free radical scavenging properties	Budin *et al.*[43]
Ligustrum lucidum (Oleaceae)	Fruits	Aqueous extract	30 g/kg/day by gavage/ for 110 days	STZ-induced diabetic rats	-	Treatment of extract Increased serum level of LH, FSH and testosterone. It counteracted the damaging effect of diabetes on spermatogenesis	Feng *et al.*[44]
Mucuna pruriens (Leguminaceae)	Seeds	Ethanolic extract	200 mg/kg b.wt./day, orally for 60 days	STZ-induced diabetic rats	Significant decrease in blood glucose level	Significantly increased serum levels of FSH, LH, and testosterone concomitantly with significant improvement in sexual behavior, libido, potency and sperm parameters	Suresh and Prakash[45]
Musa paradisiaca (Musaceae)	Root	Hydro-methanolic (40:60) extract	200 mg/kg b.wt./twice a day, orally for 28 days	STZ-induced diabetic rats	Significantly decrease fasting blood glucose and HbA1c levels and increase insulin level	Significantly increased reproductive organo-indices, epididymal sperm count, sperm motility and serum testosterone level and testicular cholesterol level as compared to diabetic rats. Extract treatment also corrected oxidative stress marker and pro apoptotic m-RNA expression pattern. These effects suggest that the plant has a promising antihyperglycemic and antioxidative activity for curing diabetes induced reproductive disorders	Chatterjee *et al.*[46]
Nigella sativa (Ranunculaceae)	Seeds	Fine powder	200 mg/kg of diet/mixed in diet	ALX-induced diabetic rats	Significant decrease in plasma glucose level	A significant increase in reproductive organ weights, improvement in semen quantity and mobility, serum testosterone level and activities of antioxidant enzymes in reproductive organs was noticed. These effects may be due to the antioxidant and androgenic effects of its phytoconstituents	Ghlissi *et al.*[47]
Ocimum gratissimum (Lamiaceae)	Leaves	Ethanolic extract	200 mg/kg b.wt./day, orally for 28 days	STZ-induced diabetic rats	-	Significant improvement in seminiferous tubules was observed, as numerous boundary cells as well as Sertoli cells were present in their lining epithelium. These protective effects may be due to the high level of alkaloids, flavonoids and also tannins found in the extract	Asuquo *et al.*[48]
Pseudocedrela kotschyi	Roots	Ethanolic extract	250 and 500 mg/kg b.wt./day, orally for 4 weeks	ALX-induced diabetic rats	Significant decrease in plasma glucose level	A significant increase in the body, testes and epididymis weights, serum testosterone levels, sperm count and motility, testicular GSH, CAT, SOD and GPx levels was observed. However, there was a significant decline in MDA levels as compared to diabetic rats.	Ojewale *et al.*[49]
Seasamum indicum (pedaliacae)	Seeds	Aqueous extract	100 mg/kg b.wt./day, intraperitoneal for 6 weeks	STZ-induced diabetic rats	Significant decrease in blood glucose level	Significantly increased serum levels of FSH, LH and testosterone. Improved testicular tissue damage by protection of spermatogenic cells and Sertoli cells and decreased cell apoptosis. These effects might be due to protective effect of extract against oxidative stress-induced impaired testicular functions in diabetic rats	Khaneshi *et al.*[50]

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Plant (family)	Part used	Extract	Dose/mode/duration	Animal models	Effect on blood glucose, insulin	Effects observed on reproductive functions	References
-	Seeds	Oil	5% and 10% oil enriched diet for 56 days	STZ-induced diabetic rats	No significant change in blood glucose level	Supplementation of diet with 5% oil improved sperm progressive motility and number of live sperm. However, incorporation of 10% oil in diet had no effect on these parameters. A significantly increase in the weight of epididymis, Leydig cells/tubule and the germ cell to Sertoli cell ratio was also observed in both 5% and 10% oil fed groups. Plasma testosterone level showed elevation in dose dependent manner. The results of this study showed that incorporation of sesame oil in to the diet may improve reproductive parameters at the level of testicular microstructures and testosterone biosynthesis	Abbasi *et al.*[51]
Spirulina maxima (Oscillatoriaceae)	Whole plant	Aqueous extract	200 mg/kg b.wt./day, orally for 14 and 28 days	STZ-induced diabetic rats	Significantly lowered blood glucose level	Treatment caused a significant increase in the testis weight, number of normal seminiferous tubules, Leydig cells, testosterone levels and seteroidogenic enzymes m-RNA. However, oxidative stress gene (Prdx4) m-RNA was decreased. These effects might be due to presence of essential nutrients in Spirulina which prevents testicular damage by lowering the blood cholesterol, glucose and improvement of steroidogenesis and antioxidant defence mechanism	Nah *et al.*[52]
Urtica dioica (Urticaceae)	Leaves	Hydro-alcoholic extract	100 mg/kg b.wt./day, orally for 5 day (prior to STZ) after 5 weeks of STZ treatment	STZ-induced diabetic rats	Significant recovery of fasting blood glucose level and regeneration of β-cells	Showed protective effect against histomorphometric alterations in seminiferous tubules as compared to diabetic control rats. The protective effects might be due to its phenolic compounds especially flavonoids in the extract which exerts antioxidant activity	Golalipour *et al.*[53]
Urtica pilulifera (Urticaceae)	Leaves	Methanolic extract	1.0 and 2.0 g/kg b.wt./day, orally for 4 Weeks	STZ-induced diabetic rats	Significantly decreased the serum glucose level	Significantly increased the levels of testosterone in both serum and testis and improved sperm count and motility. The effects may be due to antioxidant activities of bioactive compounds in the extract which might reverse the toxic action of STZ and thus restoring β-cells integrity and metabolic function	Irshaid and Mansi[54]
Vernonia amygdalina (Asteraceae)	Leaves	Ethanolic extract (80%)	200 mg/kg b.wt./day, orally 28 days	STZ-induced diabetic rats	-	Histoarchitecture of the testes showed slight improvement as indicated by presence of few Sertoli cell and spermatogenic cells. However, few vacuoles were observed in seminiferous tubules. These effects may be due to antioxidant activity of the extract	Asuquo *et al.*[48]
Withania somnifera (Solanaceae)	Roots	-	Mixed in food at ratio of 6.25%. for 4 weeks	STZ-induced diabetic wistar rats	No significant change in serum glucose level	Significant increase in serum levels of progesterone, testosterone and LH and a decrease in FSH were observed. These results may be due to presence of steroidal lactone in the extract which shows steroidal hormone mimetic activity	Kiasalari *et al.*[55]

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Plant (family)	Part used	Extract	Dose/mode/duration	Animal models	Effect on blood glucose, insulin	Effects observed on reproductive functions	References
Zingiber officinale (Zingiberaceae)	Rhizome	Aqueous extract	100 mg/kg b.wt./day, orally for 4 weeks	STZ-induced diabetic rats	-	Significant increase in epididymal sperm concentration, motility, viability and total blood antioxidant capacity in extract treated diabetic rats as compared to controls. These protective effects may be due to strong antioxidant activity of the extract	Nassiri *et al.*[56]
	Roots	Ethanolic extract	250 and 500 mg/kg b.wt./ day through orally for 65 days	ALX-induced diabetic rats	Significantly decreased serum glucose with an increase in insulin level	Significantly increased the weight of testes, seminal vesicle and the epididymal sperm progressive motility, count, viability and serum testosterone level as compared to diabetic control. Seminiferous tubules also revealed normal structure. These ameliorative effects may be attributed by antioxidant, androgenic and/or antidiabetic activity of the extract	Hafez[34]
	Roots	Methanolic or watery extract	Methanolic 100 and 200 mg/kg or watery 150 and 300 mg/kg b.wt./day, orally for 65 days	ALX-induced diabetic rats	-	Treatment of both extracts resulted in increased fertility index, sexual organs weight, serum testosterone level and epididymal sperm motility and count, with an alleviation of the lesions in the testes	Shalaby *et al.*[57]
Polyherbal drugs							
Hibiscuus sabdarifa (Malvaceae)+*Carica papaya* (Caricaceae)+ *Citrus paradassi* (Rutaceae)+*Psidium guajava* (Myrtaceae)+	Calyx Fruits Fruits Leaves	Blended aqueous extract	Mixed extract (ratio 4:3:1:2) 2.5 and 5 ml/kg b.wt./day, orally for 2 weeks	ALX-induced diabetic rats	Resulted in a significant decrease in blood glucose level	Significant increase in epididymal sperm count, sperm motility and testicular antioxidant activities (GSH, SOD, CAT) along with a reduction in MDA levels was observed. These results indicate protective potential of the blended extract against sperm and testicular toxicity in diabetic rats	Erukainure *et al.*[58]
Musa paradisiaca (Musaceae)+*Coccinia indica* (Cucurbitaceae)	Root Leaves	Hexane fractions of Hydro-methanolic extract (2:3)	Mixed extract (ratio 1:3) 2 mg/kg b.wt./day through gavage for 45 days	STZ-induced diabetic rats	Significantly decreased fasting blood glucose level and restored serum level of insulin	The number of giant cells and apoptotic germ cells in seminiferous tubules were significantly decreased. Serum testosterone level, sperm count and sperm viability and antioxidant defense parameters in testes were significantly restored. These results suggest that the extracts contains active ingredients with the capacity to correct diabetes induced reproductive dysfunction by regeneration of pancreatic β-cells and/ or recovery of oxidative stress injury	Mallick *et al.*[59]
Musa paradisiaca (Musaceae)+*Tamarindus indica* (Caesalpiniaceae)+ *Eugenia Jambolana* (Myrtaceae)+ *Coccinia indica* (Cucurbitaceae) (MTEC)	Root Seed Seed Leaves	Aqueous-methanolic (40:60) extract	Mixed extract (ratio 2:2:1:1) 60 mg/kg b.wt./two times a day for 14 day	STZ-induced diabetic rats	Significant protection in fasting blood glucose and serum insulin level	Significant recovery in testosterone levels along with correction of testicular peroxidase, catalase activities as well as TBARS and conjugated diene was noticed. Epididymal sperm count and viability, Leydig cell nuclear area and seminiferus tubular diameter were also elevated. An increase in the activities of androgenic key enzymes was also observed. The effects may be due to regeneration of β-cells, elevation in androgenic key enzymes and protection against testicular oxidative stress	Mallick *et al.*[60]

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Plant (family)	Part used	Extract	Dose/mode/duration	Animal models	Effect on blood glucose, insulin	Effects observed on reproductive functions	References
Vernonia amygdalina (VA) (Asteraceae)+*Ocimum gratissimum* (OG) (Lamiaceae)	Leaves	Ethanolic extract	200 mg/kg of VA+100 mg/kg of OG/b.wt./day, orally for 28 days	STZ-induced diabetic rats	-	Seminiferous tubules filled with active spermatids and a significant increase in number of Leyding cells was observed. These effects suggest antioxidant properties of the phytoconstituents of extracts of both plants that mop up free radicals produced by STZ	Asuquo *et al.*[48]
	-	Methanolic extract	200 mg/kg of VA+100 mg/kg of OG/b.wt./day, orally for 2 weeks.	STZ-induced diabetic rats	-	Serum levels of testosterone, FSH and LH were significantly increased. Histological studies of testis showed slight restoration of testicular architecture	Agbai *et al.*[61]
	Leaves	Ethanolic extract	100 mg/kg of VA and 200 mg/kg of OG/b.wt./ day, orally for 6 weeks	STZ-induced diabetic rats	Significant decrease fasting blood glucose level	Significant improvement of testicular architecture. Increase in Leydig cells and well define seminiferous tubules with active spermatids. These preventive changes might be due to antioxidant activities of the extract mixture	Joyce *et al.*[62]

ALX=Alloxan, b.wt=Body weight, CAT=Catalase, FSH=Follicle stimulating hormone, GSH=Glutathione, LH=Luteinizing hormone, LDH-C4=Lactate dehydrogenase-C4, MDA=Malonaldehyde, ROS=Reactive oxygen species, SOD=Superoxide dismutases, STZ=Streptozocin, TAC=Total antioxidant capacity, TBARS=Thiobarbituric acid reactive substances

advanced glycation end products and their receptors (RAGE) leading to deterioration of sperm quality, sperm functions coupled with changes in testicular metabolite levels and spermatogenic gene expression.[19-21] Several studies have shown that antioxidant treatment improves glycemic index, reduces diabetic complications, and protects components from oxidative damage.[22,23]

The use of plants in the management of diabetes is well documented, which is primarily due to anti-hyperglycemic and/or oxygen radical scavenging of their various phytoconstituents through various mechanisms.[24,25] Medicinal plants provide better alternatives as they are less toxic, easily available and affordable.[26]

A brief review of the medicinal plants having ameliorative effects on blood sugar levels and/or male reproductive functions in experimental diabetic animals is presented in Table 1.

CONCLUSION

From the results of the above studies, it can be concluded that supplementation of medicinal plant products, extracts, or herbal formulations may be useful in alleviation of DM-induced complications, especially male reproductive dysfunction, by virtue of their antidiabetic, antioxidant, and androgenic activities of various bioactive phytoconstituents.

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