**Complications in male reproductive health due to diabetes mellitus and potential herbal remedies**

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**ABSTRACT**

Between 10% and 25% of couples who are of reproductive age have infertility. Ten to thirty percent of these cases of infertility are solely ascribed to male issues. Male fertility is caused by a lot of disorder. Diabetes Mellitus is one of them which is a persistent, non-communicable disease.

As of 2014, 422 million people worldwide, or 9% of the population, are affected. It is typified by hyperglycemia, which may arise from the target tissue losing its sensitivity to insulin or the inability of pancreatic beta cell to secrete insulin. Two detrimental effects of DM are the Reactive Oxygen Species (ROS) formation and the consequent appearance of oxidative stress.

 The mechanisms involved in male sexual activity have been linked to DM, which has been shown to lower testosterone, FSH, and LH levels, decrease seminal total antioxidant capacity, increase sperm DNA damage, mitochondrial DNA fragmentation, cellular apoptosis, and decrease the activity of Leydig and Sertoli cells.

Given the foregoing, the aim of this chapter is to make a quick overview of DM and to identify and clarify the potential pathways affecting male fertility that DM affects.

**Keywords**: Diabetes, Male infertility, Herbal plant, Non-communicable disease

1. **INTRODUCTION**

Diabetes is a chronic, long-term medical disorder that creat impact on body’s ability to use food as fuel. Most of the food we take is transformed into end-product glucose or sugar molecule, by the body. Increasing in blood sugar level causes release of insulin from pancreas , enabling our cells to convert the sugar into energy that can be used by the body. Individuals who have diabetes are unable to use insulin properly or create adequate amounts of it. Consequently, the blood sugar level rises, leading to serious health problems such as heart disease, kidney illness, vision loss, and other conditions.
Diabetes comes in several forms like type 1 DM or IDDM or Insulin Dependent Diabetes Mellitus, type 2 DM or NIDDM or Non-Insulin Dependent Diabetes Mellitus, and gestational Diabetes Mellitus that appear during pregnancy. It is thought that IDDM is mainly caused by autoimmunity which disrupts body's ability to insulin production. About 5–10% of instances of diabetes are type 1 diabetes or IDDM. Generally it is diagnosed in teenagers, adolescents and young adults, and there is currently no known treatment to avoid the sickness. 90-95% of instances of diabetes are non-insulin diabetes. People with this type of diabetes experience challenges in managing their blood sugar levels and using insulin effectively. This chronic condition can be postponed or even prevented by maintaining a healthy lifestyle (CDC,2023).

Several pathophysiological mechanisms contribute to the development and advancement of diabetes, including mitochondrial dysfunction , endoplasmic reticulum (ER) stress, high blood glucose levels (hyperglycemia), elevated levels of cholesterol, triglycerides, or both (dyslipidemia), high blood pressure (hypertension), chronic inflammation and oxidative stress. All these mechanisms interact with one another, resulting in major vascular disease, microangiopathy, and neuropathy, causing numerous organ damage, malfunction, and sometimes failure across the body (Defeudis et al.,2022).

Males of childbearing age are more likely to have diabetes mellitus (DM), and the incidence of DM is directly linked to a decrease in fertility. (Hamilton and Ventura,2002,Lutz W.,2006). Moreover, an increasing percentage of infants and adolescents suffer from Diabetes Mellitus (Silink M,2002). The growing number of DM2 diagnoses under 40 years old is concerning as it increases the risk of hyperglycemia and long-term consequences(Lascar et al.,2018). Evidence suggests that young-onset diabetes accelerates the loss of β-cell function, with a 31% rise in prevalence among those aged 10-19 years.(Lascar et al.,2018). As a result, these epidemiological findings imply that diabetes develops prior to the desire to become a parent.

Diabetes can have a negative impact on men's reproductive abilities. Although it may not render you completely infertile, it does have a few affects on your fertility that make you less fertile. Men with diabetes frequently face sexual issues such as inability to firm erection and dry ejaculation. These conditions might lead to a loss of sexual interest and experiencing problems in giving birth to a child. Additionally, they produce fewer and of lower-quality sperm than typical males.

The study found that when sperm quality for infertility was compared between men with diabetes and those without the disease, the men without diabetes had 25% higher semen levels than the men with diabetes who were infertile. Additionally, diabetic males have higher DNA damage in their sperm. Overall, it demonstrates that having diabetes might make it difficult for a man to conceive a kid, as well as a higher chance of abnormalities and miscarriage to the new born.

**2. DIABETES AND MALE FERTILITY**

2.1 Type 1 diabetes and male fertility

When we have Type I Diabetes, our body attacks the cells that produce insulin, which makes it harder for us to control our blood sugar levels. As a result, we require daily exogenous dosages to augment our body's supply of insulin. Men with this illness cannot conceive and are at risk of losing their fertility.

2.2 Type 2 diabetes and male fertility

The main cause of this disorder is insufficient insulin production in the body. But if you exercised frequently and ate a balanced diet, you could manage it. Men don't need any medical assistance to become pregnant if they have complete control over it (Vareesh Kumar).

**3. DIABETES INDUCED MALE INFERTILITY**

Men with diabetes frequently have a variety of sexual problems, which are exacerbated by deteriorating physical health and waning psychological reactions (McMahon CG,2006). Several studies have explored and documented the range of diseases commonly experienced by diabetic men, along with the associated reproductive abnormalities. Here some of the most important evidence describing the effect of Diabetes Mellitus on male reproduction, in both human and animal models ,were presented -

3.1 Endocrine disorders and their effects on spermatogenesis

In normal conditions, the hypothalamus stimulates the anterior pituitary to produce luteinizing hormone (LH) and follicle stimulating hormone (FSH) by secreting gonadotropin-releasing hormone (GnRH). Now follicle stimulating hormone and luteinizing hormone induce Sertoli cells and Leydig cells to promote mature sperm production (spermatogenesis) and testosterone and dihydrotestosterone secretion accordingly.

The spermatozoa get energy by glycolysis and/or oxidative phosphorylation. For energy production they are also enabled to utilize exogenous hexoses like glucose, fructose, and mannose etc. and smaller substrates such as lactate, citrate etc. (Ballester et al.,2004). Spermatozoa are very sensitive to hormonal variations as they secrete their own insulin (Carpino et al.,2010). As a result, this insulin sensitivity in Diabetes Mellitus disrupts the endocrine pathway (negative feedback mechanism) and weakening male reproduction.

Several experiments on animals with induced hyperglycemia have exhibit that induced diabetes effect in male reproductive life with decreased vacuolization of Sertoli cell (Roessner et al.,2012), reduce sperm count (Cameronet al.,1990,Jelodaret al.,2009,Rama Raju et al.,2012), make infertile (Jelodaret al.,2009,McGawet al.,2007), altered epididymis structure and solidity (Soudamani et al.,2005), decreased serum Luteinizing Hormone , Follicle-stimulating Hormone and testosterone level (Seethalakshmiet al.,1987,Scaranoet al.,2006), and lowered numbers of Leydig cells, Sertoli cells and spermatogonia (Jelodar et al.,2009).

In addition, Ballester et al.,2004 observed decreased Leydig cell count and compromised cell function in a mouse model of diabetic mellitus caused by streptozocin (STZ). The lower Leydig cell count is connected to a drop in serum LH. This also highlights that LH regulates Leydig cell production through insulin and insulin-like growth factor 1(IGF-1) signaling pathways (Baccettiet al.,2002,Yuet al.,2006). Reduced tyrosine phosphorylation and decreased expression of GLUT-3 receptors, androgen receptors, and insulin-like growth factor 1 receptors (Soudamaniet al.,2005,Mangoliet al.,2013,Navarro-Casadoet al.,2010,Mora-Esteves and Shin,2013) is the evidence of impaired cell function. Additionally, diabetes affects spermatogenesis via an FSH-related mechanism.

Insulin insufficiency in Type I diabetes affects spermatogenesis by altering blood FSH levels (Ballester et al.,2004,Steger and Rabe,1997). Decreased FSH levels result in a decrease in tubular FSH receptors, which subsequently leads to a reduced response of the seminiferous tubule epithelium to FSH stimulation. As a consequence, diabetes mellitus disrupts spermatogenesis (Ballester et al.,2004,Steger and Rabe,1997).

Glucose also play a crucial role in spermatogenesis and the spermatic acrosome reaction. This was seen when the spontaneous acrosome reaction was lowered in a glucose-free solution and quickly restarted when glucose was added (Urner and Sakkas,1996). Glucose brought into the cell via GLUTs (Lampiao et al.,2010).

With the help of GLUTs, Glucose enter into mammalian cells via specialized transporters, against concentration gradient (Scheepers et al.,2004).

GLUT8 is significantly expressed in testis and in acrosome and mid-piece of mature human spermatozoa (Schürmannet al.,2002,Gómezet al.,2006,Bucci et al.,2011,Kim and Moley,2007). In stage 1 developing spermatocytes, but not in mature spermatozoa, GLUT8 has been found in certain investigations (Schürmann et al.,2002). Energy from glucose enters the cell and is necessary for sperm motility and spermatogenesis. Sperm motility and fertilization potential are both impacted by decreasing insulin levels, which also interfere with GLUT8 action (Verena et al.,2008). This may also be connected to a reduction of gonadotropin response to gonadotropin-releasing hormone in patients with diabetes. (Baccetti et al.,2002).

 HYPOTHALAMUS

DIABETES MELLITUS

 GnRH **(-)**

 ANTERIOR PITUITARY

 FSH + LH

TESTOSTERONE

FSH & LH 

MORPHOLOGY

MOTILITY & VIABILITY

 (+) (+)

SERTOLI CELL LEYDIG CELL

 **(-)**

 TESTOSTERONE

 SPERMATOGENESIS MALE INFERTILITY

1. b.

Fig 1: a. Normal regulation of spermatogenesis b. diabetes induced male infertility

3.2. Effect of oxidative stress (OS) and advanced glycation end-products (AGE) on sperm parameter

In a study of 52 diabetic male patient on semen analysis showed a marked reduction in sperm motility, including a decrease of rapidly progressing cells count (Bhattacharya et al.,2014). Furthermore, in a study on sperm cryopreservation, sperm parameters in diabetic men were found to be significantly lower comparatively to men with autoimmune illnesses, kidney diseases, and cardiac disease (Ranganathan et al.,2002). Significant variations in sperm kinetics and shape were seen among male partners with diabetes in another investigation by Delfino et al.,2007 that looked into infertility rates. Many other studies shows that marked reduction in sperm volume, sperm motility and sperm morphology in semen analysis of diabetic men in compare to non-diabetic men (Agbajeet al.,2007,Ali and Rakkah,2007). All of these results is linked to Oxidative imbalance between the reactive oxygen species (ROS) generation and antioxidant defense mechanisms of our body (Agarwal et al.,2014). ROS is mainly produces in Leukocytes and immature spermatozoa In male reproductive system (Agarwalet al.,2014, Leclercet al.,1997). Furthermore, mechanisms characterized by recurrent mild fluctuations in cellular metabolism may lead to tissue damage during short episodes of hyperglycemia. A large body of research, for example, (Ahmed RG,2005,Rolo and Palmeira,2006), prioritize to some metabolic pathways for hyperglycemia-induced cell damage. It has been demonstrated that in hyperglycemia increased O2 - generation by mitochondria is triggering these pathways. inhibits Glyceraldehyde-3-phosphate dehydrogenase activity is inhibited by excessive O2 generation which leads to activate all the hyperglycemic damage by inducing glycolytic metabolites to these pathways (Ahmed RG,2005).Furthermore, when potent reactive oxygen species (ROS) exceed antioxidant defense capacity of seminal fluid, multiple cascades of reactions can occur which leads to sperm DNA damage, mitochondrial DNA fragmentation, altered sperm count, motility and ultimately men become infertile. Excess of Nitric oxide (NO·) is also harmful to sperm motility which is also result of oxidative stress. NO· react with superoxide (O2·-) or hydrogen peroxide (H₂O₂) to form peroxynitrite (ONOO-) or hydroxyl radical (OH·), causing oxidation of lipids and thiol proteins of sperm membrane (Yu et al.,2006). Additionally, it can reduce ATP levels, affecting sperm movement patterns.The sperm plasma membrane content high polyunsaturated fatty acid concentration that makes it sensitive to ROS  infiltration, which causes peroxidation of lipid in sperm membrane (Ding et al.,2015). It has three stages: start, propagation, and termination. During initiation of lipid peroxidation, free radicals bind with fatty acid chains to form the lipid peroxyl radical. Then this Peroxyl radicals combine with fatty acids to form free radicals and the cycle propagates. Finally, these two radicals react and make lipid breakdown (Ding et al.,2015). Furthermore, sugar oxidation by OH- has been identified as the primary cause of DNA strand breakage. Furthermore, oxidative damage can cause degradation of bases, fragmentation of DNA and protein cross-linking. A higher proportion of DNA strand breaks have found in infertile diabetic men's sperm (Singh et al.,2014). ROS-induced oxidative damage can cause apoptosis, which is also known as programmed cell death. High ROS levels damage the integrity of the mitochondrial membrane(Doegeet al.,2000, Ibbersonet al.,2002,Joost and Thorens,2001), causing damage of mitochondrial DNA and consequently affecting sperm function .Increased reactive oxygen species (ROS) production has also been concerned with the formation of advanced glycation end-products (AGEs) which are formed under hyperglycemic conditions through non-enzymatic reactions between sugars and amino groups in proteins, lipids, and DNA (Singh et al.,2001,Unoki et al.,2007). This can disrupt macromolecules' normal function either directly by creating ROS on their own, or indirectly by activating advanced glycated end product receptors (RAGEs)(Yamagishi S,2008) . AGEs may play a vital role in causing injury and mediating damage to diabetic men's reproductive systems(Karimi et al.,2011). The RAGE is a ligand-binding receptor that causes cellular malfunction in inflammatory illnesses like diabetes. In normal tissues, RAGE expression is modest. However, in diseases such as diabetes, excessive expression causes tissue damage (Chavakiset al.,2004,Schmidtet al.,2001). In immunohistochemical studies of 21 diabetic male’s testes, epididymis, and spermatozoa of indicated a more widespread distribution of RAGE throughout the reproductive tracts of them (Mallidis et al.,2007). The seminiferous epithelium of diabetic men's testes showed a higher predominance of immunoreactive cells, while the epididymis section exhibited varying degrees of RAGE immunoreactivity. Furthermore, elevated RAGE expression was found in the acrosomal cap of spermatozoa from these males, with detailed exploration of RAGE localization during different stages of the acrosome reaction (Karimi et al.,2011). It shows that glycation processes play a significant role in sperm nDNA damage and cellular damage (Mallidiset al.,2007,Karimi et al.,2011). Additionally, research has demonstrated that seminal plasma contains vital antioxidant mechanisms that help create a protective environment for spermatozoa against oxidative stress (OS) (Yu et al.,2006). However, diabetic males typically demonstrate substantially decrease seminal total antioxidant capacity (TAC) values compared to their non-diabetic male. Another study found that increasing ROS levels result in decreased TAC levels (Mahfouz et al.,2009). The lower TAC level in DM is associated with increased malonaldehyde levels, implying that AGEs may play a role in promoting lipid peroxidation.

DIABETES

HYPERGLYCEMIA

CHANGES IN CELLULAR METABOLISM,TISSUE DAMAGE etc.

GENERATION OF ROS

seminal total antioxidant capacity (TAC)

malonaldehyde levels

sperm DNA damage, mitochondrial DNA fragmentation,apoptosis

MALE INFERTILITY

Fig 2: ROS induced male infertility due to diabetes

3.3. Diabetic neuropathy

Diabetic neuropathy (DN) affects approximately 50% of Diabetic patients. DN is classified into autonomic neuropathy or peripheral neuropathy based on whether it affects the autonomic nervous system or peripheral nerves.Both types of neuropathies causes autonomic neuropathy. Additionally, this dysfunction leads to peripheral neuropathy. As the autonomic nervous system (ANS) regulates the sexual response cycle, autonomic neuropathy due to diabetes leads to reduced sexual response, erectile dysfunction (ED), and retrograde ejaculation.(Raskin et.al.,2004) .

3.3.1. Reduced sexual response

Male sexual response begins with physical or psychological stimuli, triggering vasodilation and enhanced blood flow to the penis. Diabetes has been linked to decreased libido, which often worsens as the disease advances (Fairburn et al.,1982). Diabetes mellitus (DM)-related physical and psychological sensitivity to decrease may be linked to a decline in sexual response or desire. For instance, Fairburn et al.,1982 discovered that over a third of diabetic participants in their study did not experience the typical pumping sensation following ejaculation. Rather, before or during an orgasm, these people reported having sperm flow from their erect or flaccid penis.

3.3.2. ED

Erectile dysfunction (ED) affects millions of men and is more commonly observed among diabetic males. However, the prevalence of ED varies depending on factors such as the study population, as well as the definitions and methodologies employed in research (Thorve et al.,2011). For instance, studies have estimated the prevalence of erectile dysfunction (ED) among adult males (over 18 years old) to be 41.3% in France, 33.2% in Brazil, and 41.8% in China (Goldstein et al., 2017). In Germany, the prevalence ranges from 18.0% to 48.0% among middle-aged men (Englert et al., 2000), while around 50.0% of aging diabetic men (aged 56-85) in the United States are affected by ED (McKinlay JB,2000). Neurotransmitters, particularly nitric oxide (NO), are often produced from either the penile nerve terminals or the endothelium during regular sexual activity which causes the cavernosal arteries and surrounding smooth muscles to relax. This process stimulates penile arterial blood flow, resulting in an erection. On the other hand, endothelium-dependent smooth muscle function and the autonomic mechanism that facilitates corpora cavernosa relaxation are often impaired in males with diabetes (Carpino et al., 2010). Furthermore, a decrease in nitric oxide (NO) generation and activity at the endothelium level is a sign of endothelial dysfunction, which is linked to erectile dysfunction (Agarwal et al., 2006; Bivalacqua et al., 2003)

3.3.3. Retrograde ejaculation

The expulsion of semen into the prostatic urethra initiates a cascade of reflex activities mediated by sensory nerves within the prostatic urethra. These activities stimulate the sacral and lumbar regions of the spinal cord, which then transmit impulses through autonomic and somatic pathways, culminating in ejaculation. Retrograde ejaculation in diabetes mellitus (DM) occurs due to dysfunction of the autonomic nervous system (ANS), resulting in the inability to maintain constriction by the external urethral sphincter and other ejaculatory reflex responses. It is characterized by the backward flow of semen into the bladder instead of being expelled through the anterior urethra.(Shen et al.,2017),resulting in the sensation of ejaculation without any semen being expelled from the penis. In these men urine collected shortly after ejaculation appears cloudy, and a post-orgasmic urine sample containing numerous spermatozoa confirms the diagnosis of retrograde ejaculation.

4. **Treatment**

Once an individual has been diagnosed with fertility issues due to diabetic complications, treatment should prioritize improving the underlying condition and subsequently addressing its consequences effectively. This may involve managing blood sugar levels effectively, addressing any hormonal imbalances, and considering assisted reproductive techniques if necessary.

The treatment of diabetes focuses on regulating blood glucose levels while avoiding hypoglycemia.

4.1. Treating with synthetic drug

Insulin administration is crucial for managing Type 1 diabetes to regulate glucose levels and prevent hyperglycemia. There are different types of insulin available, such as long-acting protein-derived insulin with a half-life of 10-48 hours and short-acting insulin with a half-life of 3-8 hours (Arthur CG & Hall J, 2017). However, treatment should be tailored to each individual.

For Type 2 diabetes management, maintaining a healthy lifestyle, controlling diet and exercise, weight loss, and using appropriate medications are effective. Medications like thiazolidinediones and metformin enhance tissue sensitivity to insulin. Thiazolidinediones increase insulin sensitivity in tissues, while meglitinides and sulfonylureas stimulate insulin production by the pancreas.

Metformin is well-known for treating Type 2 diabetes by improving insulin sensitivity and regulating glucose levels (Kaul et al., 2015). Interestingly, research suggests metformin may also benefit Type 1 diabetes management. Studies on diabetic mice indicate metformin increases sperm count, testicular growth, and testosterone levels, potentially through enhanced leptin levels and Ob-R receptor expression in testes (Annie et al., 2020; Nna et al., 2019).

Medications like Avanafil (Stendra), Sildenafil (Viagra), Tadalafil (Cialis), and Vardenafil (Levitra, Staxyn) are commonly used to treat erectile dysfunction.

 4.2. Antioxidant therapy

Antioxidants act by interrupting the oxidative chain reaction and reducing or eliminating the production of reactive oxygen species (ROS)(Bansal and Bilaspuri,2011). Hughes et al.,1998 demonstrated that non-enzymatic antioxidants such as ascorbic acid (600 μmol/L), alpha-tocopherol (30 and 60 μmol/L), and urate (400 μmol/L) effectively safeguard sperm DNA integrity during in vitro fertilization (IVF).

Antioxidant therapy is still hotly contested, however studies on its use for treating OS-related male infertility have shown improvements in sperm quality and increased success rates for ART treatments (Kessopoulou E et al.,1995,Ourique GM et al.,2016,Ahmad G et al.,2016,Wong W et al.,2000) .

 4.3 Assisted Reproductive Technology (ART)

Intracytoplasmic sperm injection (ICSI) or IVF can minimise infertility in diabetic men with ejaculatory dysfunction or retrograde ejaculation. Spermatozoa from diabetic men with erectile dysfunction can be retrieved through testicular biopsy. In cases where at least one sperm is required for Intracytoplasmic Sperm Injection (ICSI) during in vitro fertilization (IVF), the collected sperm can be directly injected into the female gamete for fertilization. This approach can also be employed for diabetic men experiencing retrograde ejaculation, where spermatozoa are retrieved from post-ejaculatory urine.

Nakolettos et al.,2008 suggested that even in cases of retrograde ejaculation resistant to long-term treatment, assisted reproductive techniques (ART) can effectively manage fertilization. They reported a 51.2% fertilization rate among their study participants.

4.4 Surgery

Surgical treatments for erectile dysfunction (ED) include penile prostheses implantation and penile vascular reconstruction. Reconstructing the bladder vesical sphincter is one surgical approach that can be used to repair retrograde ejaculation (Cakiroglu et al.,2017).

**4.5 Treating with phytomedicine:** Treating diabetes with herbal plants is an area of interest for many, but it's important to note that scientific evidence supporting their effectiveness is often limited. Here are some herbal plants that have been traditionally used and studied to some extent for their potential in managing diabetes (Rao et al., 2010):

**Bitter Melon (*Momordica charantia*)**: Bitter melon is known for its hypoglycemic effects. It contains compounds that mimic insulin and may help lower blood glucose levels.

**Ginseng**: Both Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*) have been studied for their potential to improve insulin sensitivity and lower blood sugar levels.

**Cinnamon**: Cinnamon has shown promise in improving insulin sensitivity and reducing blood glucose levels. It may also lower cholesterol levels in people with diabetes.

**Fenugreek**: Fenugreek seeds contain soluble fiber, which can help lower blood sugar levels by slowing down carbohydrate digestion and absorption.

***Gymnema sylvestre***: This herb has been used in traditional medicine to lower blood sugar levels by blocking sugar absorption in the intestines and stimulating insulin production.

**Aloe Vera**: Aloe vera gel and juice may help lower blood glucose levels and improve insulin sensitivity.

**Berberine**: Although not a plant itself, berberine is a compound found in several plants (e.g., goldenseal, Oregon grape) and has shown potential in improving glucose metabolism and insulin sensitivity.

It's crucial to consult with a healthcare provider before using herbal remedies, especially if you have diabetes or other health conditions. Herbal treatments can interact with medications and may not be suitable for everyone. Additionally, they should complement, not replace, standard medical care and lifestyle interventions such as diet and exercise.

4.5.1Resveratrol (RES)

RES (resveratrol) is a polyphenol compound known for its potent antioxidant properties. Research has demonstrated that RES can improve blood glucose levels in Type 1 diabetes (T1D) rats. Furthermore, it has been shown to enhance both quantitative and qualitative sperm parameters in diabetic conditions, including sperm count, morphology, and mitochondrial activity in the sperm sheath. (Simas et al. 2017). Resveratrol increased sperm count and motility in adult diabetic rats induced with streptozotocin and nicotinamide. Moreover, it exhibited a dose-dependent beneficial effect on DNA structural integrity compared to the untreated group. (Bahmanzadeh et al. 2019) .

4.5.2 Chinese herb

Dioscorea zingiberensis (DZ) is a traditional Chinese herb that has been shown to improve the integrity of the blood-testis barrier (BTB) and reduce oxidative stress by activating proteins including ZO-1 and Nrf2 (Zhou et al., 2020) .
Conversely, gynura procumbens (GP) is known for its anti-inflammatory and anti-hyperglycemic qualities. Moreover, it has been demonstrated to upregulate the expression of genes for proteins related to sperm maturation and sperm-egg contact (Kamaruzaman et al. 2018).

5. **Conclusion**

Lower male fertility is associated with diabetes. Research has determined the several routes contributing to this condition. The processes encompass AGE generation, OS development, GLUT8 activity alterations, endocrine disruption, and the frequency of DN. Physicians and reproductive endocrinologists must inform their patients about the possible effects of diabetes mellitus (DM) on male fertility, even though they should closely consider the effects of DM in their plans for fertility treatment.

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