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The role of hyperglycaemia, oxidative stress, and inflammation in diabetes-related male infertility: Therapeutic properties of medicinal plants

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ABSTRACT

The prevalence of diabetes mellitus (DM) continues to rise at an alarming rate. DM leads to a decline in male reproductive function. Hyperglycaemia is an instigator of both oxidative stress and inflammation in the male reproductive system. The presence of excessive reactive oxygen species (ROS) and inflammatory markers in the semen of diabetic individuals results in the decline of sperm parameters. Despite ongoing advancements in the treatment of DM with conventional drugs, concern about treatment costs and side effects is high. Scientific research focus has therefore shifted to investigating naturally occurring safer, cheaper, and more effective treatments. This review outlined the link between hyperglycaemia and diabetic complications, and the role of oxidative stress and inflammation in the development of male infertility. We also reviewed the effects of phytochemicals in medicinal plants in treating DM-related male infertility. This review concluded that oxidative stress and inflammation are instigators of the decline in sperm parameters in diabetic conditions. The administration of medicinal plant extracts with hypoglycaemic, anti-diabetic, antioxidative, and anti-inflammatory properties can potentially restore diabetic-related male reproductive dysfunction.

Implication for health policy/practice/research/medical education:
This review outlined the role hyperglycaemia in the occurrence of oxidative stress and inflammation in diabetes-related male infertility. Thereafter, medicinal plants and their phenolic compounds were reviewed as potential therapeutic interventions in the treatment of diabetes-related male infertility.

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Introduction

Complications, such as nephropathy, cardiovascular diseases, neurodegenerative diseases, and reproductive dysfunction, are known to accompany the manifestation of diabetes mellitus (DM) due to hyperglycaemia (1). DM is a social and economic burden globally and one of the leading causes of mortality (2). Approximately 463 million people worldwide are affected by DM (3) and its incidence continues to rise at an alarming rate (1,4). The global prevalence is estimated to reach 700 million people that would be affected by DM by 2045 (1,4). Amongst the aforementioned complications accompanying DM, male infertility continues to rise due to the decline in sperm quality caused by hyperglycaemia-induced oxidative stress (OS) and inflammation (5).

The rise in male infertility poses a great social and economic concern in couples (6). It is, therefore, crucial to treat DM and its underlying complications that lead to male reproductive dysfunction. The increased interest in drug therapy search for the treatment of DM complications is due to the flaws such as adverse effects and cost, accompanying the use of conventional drugs (7). Research has shifted the search for an efficacious, inexpensive, and safe treatment for DM towards medicinal plants (8).

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Both OS and inflammation are manifestations of DM, and their amelioration can reduce DM complications such as male infertility (5).

Among many, polyphenols (mainly flavonoids) have been recorded as potent free radical scavenging agents in ameliorating OS and some acids, such as hydroxycinnamic and coumaric acids, are well known for their antioxidant and anti-inflammatory activities (9). Medicinal plants such as *Turnera diffusa*, (5) *Retama raetam* (10), *Garcinia livingstonei* (11), and red onion (12), and phytochemicals such as flavonoids, flavones, and phenolic acids have been reported for their potential benefits in the treatment of DM complications (13). Although many medicinal plants have been identified, reported, and documented their anti-diabetic effects in traditional medicine, in-depth knowledge of their mechanisms of actions is vital to maximising efficacy and effectiveness. The current study reviews the course of DM development from hyperglycaemia to tissue damage and male reproductive dysfunction. This review explains the link between hyperglycaemia, OS, inflammation, and the decline in sperm quality. We further review the phytochemical composition of a few medicinal plants and the possible treatment of DM-related male infertility with medicinal plants.

Materials and Methods

Several databases such as Google Scholar, Elsevier, Scopus, PubMed, and ResearchGate were used to obtain information about the link between DM and male infertility, and numerous medicinal plants used in the treatment of diabetic complications. In these databases, recent (not older than 10 years) review articles, mini review articles, original articles, and book chapters were assessed. The search terms include keywords such as diabetes mellitus, male infertility, hyperglycaemia, oxidative stress, inflammation, phytochemicals, medicinal plants, and traditional medicine.

Results

The development of diabetes mellitus

The regulation of blood glucose by insulin and glucagon maintains a homeostatic balance of blood glucose (14). A disruption in insulin production, secretion, or action leads to an abnormal and prolonged increase in blood glucose level (hyperglycaemia) and an inappropriate increase in glucagon (15). The impairment of the glucose metabolism homeostatic balance and an abnormal rise in blood glucose level is a characteristic of the development of DM (16). DM is a metabolic disease associated with complications arising from hyperglycaemia and consequent macromolecular disruptions (15). Both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are characterised by hyperglycaemia and impaired glucose and lipid metabolism (17).

T1DM is distinguished by its pathology arising from the deficiency of insulin in the plasma, which is mostly caused by the autoinflammation of the pancreas (1). T2DM is the most common type of DM (90% of diabetic cases), characterised by insulin resistance (3). Although sufficient insulin is present in the plasma, insulin action is impaired due to the insensitivity of insulin receptors (15). Excessive plasma insulin leads to further worsening of insulin resistance and dysregulation of glucose metabolism (18).

Among several causative factors associated with the development of DM, such as genetic, lifestyle and environmental factors, obesity remains an important role player in DM morbidity (19,20). Obesity occurs when excessive energy and fats accumulate due to high-calorie intake, physical inactivity, or genetic factors (21). At the onset of DM, the accumulation of excess adipocytes around the pancreas leads to the destruction of the β-cells of Langerhans and reduces the level of insulin produced and secreted (1). In both the onset and the course of DM development, an uncontrolled increase in calorie intake increases the accumulation of triglycerides and hypertrophy of fat cells and increases the risk of insulin resistance, subsequently leading to uncontrolled hyperglycaemia (1). The accumulation of fat around muscles and the liver also causes insulin insensitivity (22).

Fat accumulation in obese individuals leads to the secretion of inflammatory markers by adipocytes, which leads to the inflammation of the pancreas and other organs, leading to insulin resistance and the reduction of insulin secretion, hence the resulting hyperglycaemia (19). Complications such as male infertility, accompanying DM and metabolic syndrome are also alluded to obesity (23). While obesity leads to insulin insensitivity and hyperglycaemia, the accumulation of fats in male subjects around the testes increases temperature and is detrimental to spermatogenesis (23). In correlation to these findings, it was deduced in a similar study that physical activity improves semen parameters and ameliorates male reproductive dysfunction (24). Over the past years, the prevalence of obesity and DM has been managed by a decrease in calorie intake and increased physical activity, which maintains the glycaemic index by improving beta cell function and precluding insulin resistance (1).

The liver serves a crucial role in storing and releasing glucose in regulating carbohydrate metabolism (3). Due to the activity of glucose-6-phosphatase, which reverses the phosphorylation of glucose, the liver contributes to the increase in blood glucose levels (3). In diabetic conditions, the absence or impairment of insulin action on hepatic cells causes an increase in the release of glucose into the blood through the initiation of gluconeogenesis (15). The inactivation of glucokinase and reduction in glucose uptake during postprandial blood glucose increase has been noted in diabetic models, and it plays a causative role in the initiation of hyperglycaemia (15). In most diabetic

patients, less glycogen storage and impaired hepatic glucose production have been observed (3). The activation of glucose-6-phosphatase causes the exacerbation of hyperglycaemia in DM, and the inhibition of glucokinase and glycogen synthase, consequently leading to the efflux of glucose from the liver into the blood (15). Due to prolonged hyperglycaemia in diabetic patients, excessive glucose molecules form reactions and interactions that lead to the development of DM complications such as cardiovascular diseases, neurological degeneration, nephropathy, retinopathy, and male infertility (25). The implications of hyperglycaemia in DM are discussed in the subsections below.

Implications of hyperglycaemia

The hallmark of DM, hyperglycaemia, is the basis of subsequent complications prominent in diabetic patients. Several reactions, such as advanced glycation end-products (AGEs) formation, OS, and inflammation, dependently arise excessively in the occurrence of hyperglycaemia (4). Although the reactions mentioned above exacerbate each other, leading to continuous damage, each reaction majorly contributes to the progression of DM by instigating macromolecular and tissue damage (Figure 1) (26). This section outlines the implications of hyperglycaemia, linking DM to its consequent complications.

Oxidative stress

Overview of the oxidative balance

Oxidative stress occurs due to the dysregulation of free radicals, particularly reactive oxygen species (ROS), caused by either increased generation of free radicals, reduced capacity of the free radical-scavenging system, or both (27). Free radicals are highly reactive molecules due to their instability caused by a free electron in their outermost orbital (28). Amongst different free radicals, such as reactive nitrogen species (RNS) and reactive sulfur species (RSS), ROS are the main instigator of OS (28). Therefore, this review will refer to free radicals as ROS. Although oxygen is a fundamental physiological element, it is the primary substrate of the generation of ROS (29). The excessive generation of ROS, such as superoxide (O_2^-), hydrogen dioxide, hypochlorous acid (HOCL), lipid peroxides, and hydrogen peroxide (H_2O_2) are associated with macromolecular damage caused by the resulting OS (23).

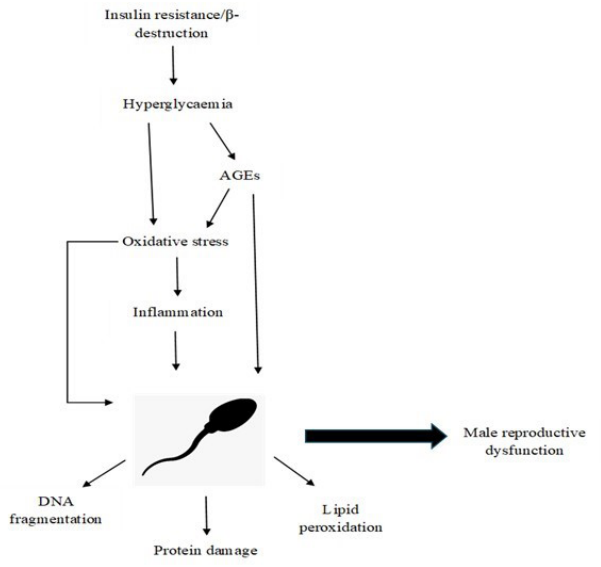

Figure 1. The link between hyperglycaemia, advanced glycation end-products (AGEs), oxidative stress, inflammation and developing male reproductive dysfunction. The increase in glucose levels caused by insulin resistance facilitates non-enzymatic reactions with proteins (formation of AGEs). Glucotoxicity leads to oxidative stress and inflammation in the semen, which reduces sperm parameters.

The presence of the typically regulated ROS is crucial in some physiological functions, such as the defence against pathogens and signal transduction under normal conditions (1). The regulation of ROS is maintained by the balance between the generation and the removal of the ROS (1). The antioxidant system consists of protein and non-protein molecules that neutralise the oxidation of other biological molecules by free radicals (27). The increase in free radicals activates the release of endogenous antioxidants to either scavenge or neutralise free radicals (27). However, antioxidants can also be obtained from diet, such as fruits and vegetables (exogenous antioxidants) (30). Some endogenous antioxidants, such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), are enzymatic and catalyse reactions that lead to the elimination of free radicals (31). Non-enzymatic antioxidants include glutathione, vitamins C and E, carotenoids, and flavonoids (28). The perturbation of the antioxidant system caused by the reduction/deactivation of enzymatic activity or the decrease in production of antioxidants caused by upstream factors such as the nuclear factor erythroid 2-relater factor 2 (NRF2), can lead to OS (28). The reaction of ROS with lipids, proteins, and DNA leads to cell death and tissue damage (28). Depending on where oxidative damage occurs, different complications arise.

The role of hyperglycaemia in oxidative stress

Amongst other causative factors of OS, such as smoking, excessive ultraviolet light, environmental pollutants, hyperglycaemia is a driving force in the generation of ROS and the development of OS (28). Hyperglycaemic-induced OS plays a role in the development of diabetic complications (32). It is therefore vital to understand the pathway through which hyperglycaemia leads to OS as a target for therapeutic interventions. Besides the direct molecular damage caused by ROS in diabetic patients, OS also exacerbates insulin resistance and increases chronic inflammation (33). Excessive generation of free radicals from hyperglycaemia occurs through the

following pathways: 1) the leaking of electrons from the mitochondria, 2) AGEs formation, and 3) the polyol pathway (1).

ROS are mainly produced in the mitochondria's electron transport chain (ETC) (29). During a critical stage of ATP formation in the ETC (oxidative phosphorylation), ROS are generated mainly from the partial reduction of oxygen caused by the electrons leaking out of the ETC (29). Due to excess glucose, glucotoxicity arises and leads to the impairment of the mitochondrial function by increasing mitochondrial membrane potential and ROS generation (1).

AGEs are products of the non-enzymatic Maillard reaction between reducing sugars (glucose) and the amino groups of proteins (34). In the early stages of the Maillard reaction, a reducing sugar such as glucose reacts with a protein to form Schiff bases (35). In the intermediate stage, further rearrangement of Amadori adducts leads to the formation of Amadori products (4). The major Amadori products, such as methylglyoxal (MGO) and 3-deoxyglucosone (DG), are important hall-markers of AGEs production (4). Further oxidation of the Amadori products leads to the final formation of AGEs (36). Besides the Maillard pathway, AGEs are formed through the polyol pathway, a bypass pathway initiated by converting glucose to sorbitol in hyperglycaemic conditions instead of channelling to the glycolysis pathway (4), as depicted in Figure 2. The accumulation of intermediate products and AGEs is the instigator of vascular damage in DM.

In normal blood glucose conditions, the production of AGEs is regulated by the production of anti-stressors (37). However, in hyperglycaemic conditions, the production of anti-stressors is exceeded by the excessive production of AGEs (4). The interaction of AGEs with proteins, lipids, and DNA is a major contributor to macrovascular and macromolecular damage in diabetic patients (38). Due to excess AGEs, cross-linkages between neighbouring AGEs are formed, and they interact and deactivate crucial proteins (39).

Proteins affected by AGEs become dysfunctional and resist degradation, becoming the agents of free radical formation and consequently leading to OS (40). The deleterious effect of AGEs is also associated with the binding of AGEs to receptors of advanced glycation end-products (RAGE), eliciting downstream signal transduction (41). The binding of AGEs to RAGEs downstream activates c-Jun N-terminal kinase (JNK), which activates IRS-1 and causes a false insulin signalling cascade and consequent insulin resistance (4).

During hyperglycaemia, excess glucose is transferred to a bypass pathway called the polyol/sorbitol pathway to physiologically compensate for the increase in glucose concentration, as depicted in Figure 2 (1). In the polyol pathway, aldose reductase uses NADPH (producing $NADP^+$) to convert glucose to sorbitol, which is further converted to fructose, catalysed by sorbitol dehydrogenase with the consumption of NAD^+ and the production of NADH (42). The sorbitol pathway leads to the excessive increase in NADH, which overloads the mitochondria and leads to increased ROS generation (42). Furthermore, the reduction in NADPH reduces the amount of GSH formed, leading to a compromised antioxidant system. Both the production of NADH and the consumption of NADPH contribute to the pathological increase of ROS and OS (43).

Inflammation

Inflammation as an immune response

Pathogens and foreign molecules elicit an immune response that subsequently leads to pro-inflammatory

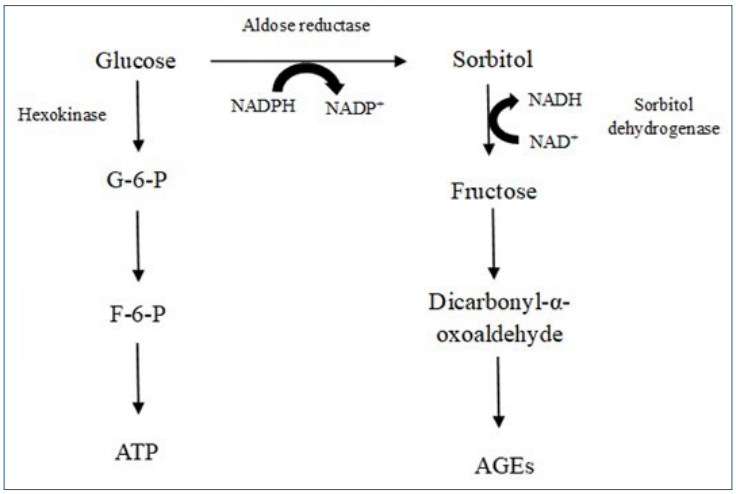

Figure 2. The overactivation of the polyol pathway in hyperglycaemia. Basal glucose is converted into glucose 6-phosphate (G-6-P) by hexokinase, which is further converted to fructose 6-phosphate (F-6-P) to produce adenosine triphosphate (ATP). Excess glucose in hyperglycaemia is converted to sorbitol catalysed by aldose reductase. Sorbitol dehydrogenase converts sorbitol to fructose with NADH as an end-product. The polyol pathway leads to the production of advanced glycation end-products (AGEs).

cytokine secretion in a normal physiological reaction called inflammation (44). Chronic inflammation occurs due to the prolonged activation of immune cells and the excessive secretion of inflammatory markers after severe and prolonged damage (45). In both stages of inflammation, immune cells such as natural killer cells, T-lymphocytes, B-lymphocytes, and macrophages are activated and mobilized to the area of damage where they secrete pro-inflammatory markers (46). The availability of inflammatory markers such as tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) also recruits more immune cells to the area of damage (46).

Nitric oxide (NO) is also an important mediator of inflammation, and its elevation is associated with tissue damage (47). The accumulation of immune cells in the injured or infected area (immune cell infiltration) leads to tissue damage (48). Inflammation is initiated by Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a transcription factor that leads to the transcription of genes that code for mediators of inflammation (49). The promotion of NF-κB activity during tissue damage or invasion by foreign material is the initial cause of inflammation, followed by the downstream expression of pro-inflammatory cytokines (50). Although inflammation is a normal physiological process to get rid of pathogens, it has been implicated in the pathogenesis of several health complications, including DM (48). Previous research focussing on the amelioration of chronic inflammation has therefore targeted the augmentation of NF-κB activity to reduce the level of inflammatory cytokines (31).

The role of hyperglycaemia in inflammation

The development of DM complications is associated with chronic inflammation (50). Hyperglycaemia leads to the activation of several inflammatory pathways and the secretion of excessive levels of cytokines (50). In addition, it has been deduced that the overall upregulation of inflammation in diabetic patients has alluded to the coupled and individual actions of obesity, hyperglycaemia, and OS (1). In DM-associated obesity, hypertrophic adipocytes secrete excessive cytokines (1). The recruitment of more cytokines from macrophages is augmented by the release of fatty acids in obese diabetic individuals (1).

As previously discussed, hyperglycaemia upregulates inflammation through the formation of AGEs. The binding of AGEs to RAGE leads to the downstream activation of IκB kinase (IKKβ), which inhibits Iκβ. This protein binds to the main regulating transcription factor of inflammation, NF-κB (4). Inhibition of Iκβ releases NF-κB, which freely exerts its effect in the nucleus, producing pro-inflammatory markers (51). The high concentration of AGEs leads to exaggerated activation of NF-κB and excessive production of inflammatory markers such as IL-1β, IL-6, and TNF-α (4). In the prediabetic stage, hyperglycaemia-induced OS activates excessive production of cytokines from adipose tissue (28). In a previous study conducted by (26), the elevation of TNF-α caused by hyperglycaemia was observed and associated with the possible subsequent upregulation of NF-κB, followed by further immune cell recruitment.

The effect of hyperglycaemia on male reproduction

The increase in infertility cases has become a global public concern, with approximately 15% of couples affected (52). Couples affected by infertility are mostly stigmatized and suffer from financial stress and depression, which ultimately leads to mental issues and overall reduced quality of life (6). Amongst the overall prevalence of infertility, over 40% of the cases are alluded to male reproductive dysfunction (53,54). Approximately 7% of male individuals are affected by male infertility globally (53). The causative factors of male infertility are not limited to obesity (55), age (6), and physical or environmental factors (23).

In obese individuals, excessive adipose tissue accumulation leads to the decrease in the production of testosterone and a decline in sperm parameters (56). Previous studies have also reported the age-related alteration and damage of testicular mitochondria, which leads to reduced ATP production and motility of sperm cells (57). The decline in male reproductive parameters has also been associated with environmental toxins from metals, food additives, and pollutants, which cause reactions with sperm cells and lead to apoptosis (58). Amongst the aforementioned causes of male reproductive dysfunction, DM has been listed as a causative factor in the decline in sperm quality and an increase in male infertility (26,40). Hyperglycaemia, resulting from the induction of DM, leads to spermatogenic dysfunction (26,40). Figure 1 shows the link between hyperglycaemia, OS, inflammation, and male infertility.

Hyperglycaemia-induced oxidative stress in male infertility

The male reproductive organs generate free radicals balanced by the available antioxidants during normal conditions (59). In normal conditions, a controlled level of free radicals produced in the plasma membrane assists in spermatogenesis processes such as sperm capacitation (24). During OS, free radicals are produced in the spermatozoa mainly through mitochondrial leakage of electrons, which ultimately react with oxygen (23). Besides the spermatozoa, immature cells and round cells such as leucocytes also contribute to the production of free radicals in the semen (53).

In hyperglycaemic conditions, excessive generation of free radicals is promoted in the testicular tissue and germ cells through the leaking of electrons of the mitochondria (59). DM and obesity are collectively factors leading to the

excessive production of free radicals and the cause of OS in male reproductive organs (23). The overload of free radicals in the reproductive organs compromises the antioxidant system and reduces antioxidant enzyme activities, leading to OS (59). In a previous study, the increase in free radicals associated with hyperglycaemia negatively correlated with the activities of antioxidants such as SOD and CAT in the semen (60). OS contributes to approximately 35% of male infertility cases globally (53). The manifestation of OS in diabetic models is a major cause of apoptosis of testicular cells (61). Accumulated free radicals lead to both lipid peroxidation of sperm cell membranes and the oxidation of sperm organelles, leading to the fragmentation of DNA, thereby reducing sperm viability and motility (62).

Sperm DNA damage is a crucial concept in male reproduction and is the leading cause of infertility in diabetic complications (61). Excessive levels of free radicals in the testes and epididymis have been reported to lead to sperm DNA damage in diabetic-related male infertility cases (61). Sperm cells are most vulnerable to lipid peroxidation due to the abundance of polyunsaturated fatty acids as part of their membranes (59). Although polyunsaturated acids in the sperm cell serve a crucial role in the fluidity of the plasma membranes, their reaction with free radicals leads to the formation of toxic end-products such as malondialdehyde (MDA), which leads to compromised cell motility and cell death (53). The presence of elevated MDA levels in diabetic semen has revealed the role of hyperglycaemia in the lipid peroxidation of sperm cells and the consequent male reproductive dysfunction (24). Sperm parameters, such as acrosomal reaction, mitochondrial membrane potential, and DNA integrity, are compromised due to OS, thus the consequent apoptosis of the sperm cells (23,59).

Hyperglycaemia-induced inflammation in male infertility

Hyperglycaemia-associated inflammation contributes to male reproductive dysfunction (26,61). Inflammation in hyperglycaemic conditions is primarily initiated by the activation of NF-κB by OS (63). Reports have shown the accumulation of pro-inflammatory cytokines in male reproductive cells and tissue of individuals with male infertility (64). Although cytokines detected in different pathologies are not specific to diseases, some cytokines are predominantly found in accompanying certain complications and are used as predictors of specific diseases (46). Cytokines such as TNF-α, IL-6, and IL8 have been primarily found in the reproductive parameters of diabetic patients (64).

In a previous study, pro-inflammatory markers IL-17 and IL-18, which are positively correlated with the above-mentioned main male reproductive cytokines, were elevated in diabetic semen samples and associated with the resulting decrease in sperm parameters such as sperm DNA integrity, sperm motility, and vitality (64). A similar study by (65) investigated the effect of DM induction in the manifestation of inflammation and the development of spermatogenetic damage. In their study, an increase in TNF-α and IL-17 in the sperm and testicular tissue of rats revealed the involvement of inflammation in diabetes-related male infertility (65). Besides causing organ damage, TNF-α is also involved in the recruitment of other inflammatory markers, such as NO, which both cause a reduction in sperm parameters and prolong inflammation by promoting immune cell infiltration and OS (26,61). Synergistic to the effect of OS, the elevation of inflammatory cytokines in diabetic conditions also causes lipid peroxidation of sperm cells, consequently leading to reduced sperm quality and possible male infertility (64).

The role of phytochemicals in medicinal plants

Following carbohydrates, phenolic compounds are the second most abundant compounds in most medicinal plants (66). Phenolic compounds in plants include but are not limited to, flavonoids (flavonols and flavanols), flavones, alkaloids, and phenolic acids (hydroxycinnamic acids, hydroxybenzoic acids). Amongst phenolic compounds, flavonoids are mostly reported as potent antioxidants (67). The structural composition of phenolic compounds (one aromatic ring attached to hydroxyl groups) contributes to their health benefits (66). Phenolic compounds are well-known for their ameliorative health benefits in the treatment of diseases associated with inflammation, OS, and microbial infection (68). Certain phenolic compounds in medicinal plants are responsible for the beneficial effect in the treatment of DM-related male infertility (10).

In our previous ethnobotanical study, we identified several medicinal plants used to treat DM and male infertility in traditional medicine practice (69). A similar study conducted by (70) revealed a vast availability of medicinal plants used in the treatment of DM complications. However, less studies have focussed on the phytochemical screening of these plants. Many other medicinal plants are recorded in the literature for their potential benefit in treating DM-related male infertility worldwide, as represented in Table 1. Countries including Nigeria, South Africa, Cameroon, China, India, and Europe appear in the literature for their scientific studies on potentially effective medicinal plants and their role in the treatment of DM-related male infertility (71-75). However, the discovery and research of more medicinal plants are paramount in discovering more effective bioactive compounds that are different in different plants. Additionally, the accessibility of medicinal plants and their status in biodiversity are important factors in choosing suitable medicinal plants. Therefore, creating a large pool of beneficial medicinal plants is necessary. More DM and male infertility studies have tested the efficacy of medicinal plants in in vivo animal models,

Table 1. Medicinal plants used in different parts of the world for the treatment of diabetes mellitus (DM)-related male infertility and other ailments

Medicinal plant	Family	Country of use	Pharmaco-active compounds	Study model	Effect in DM-related male infertility	Other medicinal use	Reference
Cleome rutidosperma	Cleomaceae	Southern Nigeria	Tannins, flavonoids, phenols	In vivo (male Wistar rats)	Reduces inflammation and OS	Relieves pain and fever, diuretic	(71,72)
Moringa oleifera	Moringaceae	Middle East Africa, Sothern Asia	2-Isopropoxyethyl propionate, Propanamide, carbonic acid, citramalic acid	In vitro (Human sperm)	Antioxidative effect	Prevents skin damage	(75,80,82)
Alpinia officinarum	Zingiberaceae	Europe	Glycosides, flavonoids, diarylheptanoids, flavonol	In vivo (male rats)	Increase in sperm quality	Anti-cancer reduces inflammation, antimicrobial, anti-ulcers, relieves pain	(74)
Anchomanes difformis	Araceae	Nigeria	Tannins, flavonoids, phenols	In vivo (Male Wistar rats)	Hypoglycaemia	Hepatoprotective	(76)
Psidium Guajava	Myrtaceae	Around the world	Quercetin	*In vivo* (Male Wistar rats)	Hypoglycaemic reduces OS	Antimicrobial effect: treats allergic reactions, relieves coughs, hepatoprotective.	(77)
Carica Papaya	Caricaceae	Mexico and Central America	Alkaloids, glycosides, flavonoids, and tannins	*In vivo* (Male Wistar rats)	Increases sperm motility	Colic, fever, Malaria, asthma	(78)
Curcuma amada	Zingiberaceae	India	Alkaloids and flavonoids	In vivo (Albino rats)	Hypoglycaemic,	Antibacterial and anti-fungal effect	(81)
Coptis chinensis	Ranunculaceae	China	Berberine, alkaloids, coumarin, tannins	In vivo (Sprague-Dawley rats)	Hypoglycaemic reduces inflammation, hypolipidaemic, antioxidative	Bowel disease, arthritis	(68,83)
Hunteria umbellata	Apocynaceae	Cameroon, Ghana, Senegal, Congo	Quercetin, apigenin, alkaloids, gallic acid, triterpenoids	Ethnobotanical study	Afrodisiac, anti-inflammation, hypoglycamic	Wound healing in leprosy, stomach-ache, menstrual complications	(73)
Ficus carica	Moraceae	Malaysia, Turkey	Anthocyanins, flavonoids, kaempferol, myricetin, quercetin	In vivo (Sprague-Dawley rats)	Hypoglycaemic improves sperm quality	Cardiovascular diseases	(84)

while less studies focussed on in vivo and in vitro human studies (76-78).

In a previous study, the antioxidant and anti-inflammatory effect of *Cleome rutidosperma*, a plant used for treating male infertility in diabetic men, was unfolded using male Wistar rats (71). In their study, the beneficial effect of *C. rutidosperma* was linked to bioactive compounds such as tannins, flavonoids, and phenols (71). In a similar animal study conducted in Europe, the effect of *Alpinia officinarum* in increasing sperm quality of diabetic rats was discovered (74). This effect was linked to glycosides, flavonoids, diarylheptanoids, and flavonol, which scavenge ROS and reduce the secretion of inflammatory cytokines in male reproductive organs (74). The frequent appearance of phenolic compounds in different medicinal plants used in treating DM-related male reproductive dysfunction, as observed in Table 1, suggests the important role of these bioactive compounds in treating diabetic complications and the improvement of male reproductive parameters. In these previous studies, it is deduced that phenolic compounds increase antioxidant capacity and antioxidant enzyme activity, thereby reducing oxidative damage in reproductive organs and cells (79,80). The presence of a bioactive compound, berberine, is linked to the reduction of inflammatory cytokines through the inhibition of NF-κB in an animal model (68). Besides the antioxidant and anti-inflammatory effect of phenolic compounds in different DM medicinal plants, some studies have deduced that different compounds such as alkaloids, flavonoids, alkaloids, coumarin, tannins and gallic acid also led to the increase in insulin sensitivity and a reduction in blood glucose levels (68,76,81).

In corroboration to this, phenolic compound-rich *Coptis chinensis* found in China was found to improve glucose metabolism in diabetic mice through the increase in the stimulation of beta cells (β-cells) to produce and secrete insulin (79). *Moringa oleifera* is also a common medicinal plant originally from Middle East Africa, India, and Southern Asia and used in different parts of the world to treat skin complications (82). The leaves of *M. oleifera* are used in these parts of the world for the treatment of DM complications, including male infertility (80). Phytochemical profiling of *M. oleifera* leaves has shown the presence of bioactive compounds such as 2-Isopropoxyethyl propionate, Propanamide, carbonic acid, and citramalic acid, which exhibit anti-inflammatory and antioxidant activities (82). *M. oleifera* also reduces lipid peroxidation by eradicating ROS in human spermatozoa and increases sperm quality (75).

In a previous study, the antioxidant effects of *Retama raetam* in the treatment of male infertility in diabetic rats were linked to the presence of flavonoids such as kaempferol, apigenin, and quercetin (10). In a similar study, the effect of red onion powder in the improvement of male reproductive function in diabetic rats was linked to profiled phytochemicals such as flavonoids, anthocyanins, quercetin glucosides, S-methyl cysteine sulfoxide (12). *Turnera diffusa* showed a protective effect in the testes of diabetic-induced rats by restoring sperm vitality, motility, and DNA integrity (85). The protective effect of *T. diffusa* was linked to the anti-inflammatory effect (downregulation of NF-κB) and the antioxidant effect (increase in antioxidant enzyme activities) potentially exhibited by phytochemicals such as p-coumaric acid, kaempferol, and protocatechuic acid (85). *Garcinia livingstonei* has also been reported for its hypoglycaemic effect in the treatment of diabetic complications through the inhibition of α-glucosidase (11). The composition of *G. livingstonei* has also been reported to contain flavonoids and benzophenones,, which can be anti-inflammatory and antioxidative (86).

In a study (59), resveratrol was reported to exhibit anti-apoptotic effects in diabetic rat sperm cells by amelioration OS, thereby reducing DNA fragmentation and mitochondrial damage. The health benefit of flavonoids in medicinal plants was confirmed in a previous study by the isolation of a biflavonoid compound, troxerutin, for the treatment of DM-related male reproductive dysfunction (87). In their study, troxerutin exhibited antioxidant effects and improved sperm quality (viability, chromatin integrity, and motility (87). The ameliorative effect of hesperidin, a flavonone, in OS was reported in a previous study (60). The free radical-scavenging activity of some plants through direct neutralisation and upregulation of antioxidant enzyme activity is associated with hydroxycinnamic acids (9).

Besides the effect of medicinal plants in cells and animal models, clinical trials have been previously conducted to investigate the potential therapeutic effect of medicinal plants on human. The oral intake of raw cinnamon has been recorded in a previous study for its postprandial hypoglycaemic effect in human (88). A similar study with 43 human participants with T2DM deduced that the oral intake of date seed controlled glycaemic index and increased antioxidant capacity (89). Although the use of synthetic drugs reduces glucose levels in diabetic patients, several medicinal plants have shown better hypoglycaemic effects. In a clinical trial the combination of different medicinal plants showed a greater glycaemic control compared to metformin (90).

Conclusion

This review gives an overall overview of how prolonged hyperglycaemia in diabetic conditions leads to glucotoxicity in male reproductive organ through the generation of excessive ROS and pro-inflammatory cytokines. Although the main instigator of tissue damage and cell death in DM is hyperglycaemia, the treatment target cannot be limited to the reduction of glucose but in the decrease of the elevated ROS and inflammatory markers. This review also

shows that most DM clinical trials in the literature focus on the reduction of glucose. The understanding of other pathological pathways involved in diabetic complications and the search for medicinal plants targeting these pathways are paramount. Many medicinal plants have been identified in previous ethnobotanical studies. However, phytochemical screening of these identified plants is paramount in discovering more compounds that can be isolated and used to treat diabetic complications. The isolation of specific therapeutic compounds can enhance the effectiveness of medicinal plants. More studies, comparing the use of existing synthetic drugs against the use of medicinal plants is paramount in the search for better treatment.

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Conflict of interests

The authors declare no conflict of interest.

Ethical considerations

Ethical approval for the study was obtained from the Cape Peninsula University of Technology Research Ethics Committee (CPUT-REC) (ethics code: CPUT/HWS-REC 2024/H9).

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