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Review

A review on some causes of male infertility

F. O. Olayemi

Department of Veterinary Physiology, Biochemistry and Pharmacology, University of Ibadan, Ibadan, Oyo State, Nigeria. E-mail: funsho_olayemi@yahoo.com, fo.olayemi@mail.ui.edu.ng. Tel: +2348034710114.

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This work reviews a wide range of factors that are responsible for male infertility. The normal human sperm cell measures 50-60 µm in length and has head, neck, middle piece and tail. The head is oval in shape and is 3-5 µm in length and 2-3 µm in width. The mid-piece is slender, straight and regular in outline. It is aligned with the long axis of the head, and is approximately 7-8 µm in length. Its width is about one third of the head. The tail is slender, straight and regular in outline and is 40-45 µm in length. The ability to fertilize oocytes is considered as the ultimate test of sperm function. A male is said to be infertile if he is unable to impregnate his partner after one year of unprotected intercourse. Some cases of male infertility are due to anatomical abnormalities such as varicoceles. This work reviewed some natural and synthetic products that have been implicated in male infertility. There is also a section on some medicinal plants that are responsible for male infertility.

Key words: Male, infertility, sperm, medicinal plants.

INTRODUCTION

Infertility is defined as the inability to achieve pregnancy after one year of unprotected intercourse (Purvis and Christiansen, 1992). Conception is normally achieved within 12 months in 80 to 85% of couples who are not using contraceptive measures; which means an estimated 15% of couples attempting their first pregnancy, may experience difficulty in conceiving. Some cases of male infertility are due to anatomical abnormalities such as varicoceles, ductal obstructions or ejaculatory disorders (Sinclair, 2000).

A normal semen sample should have a volume of 1.5 to 5ml with greater than 20 million sperms/ml. The number of abnormal sperm should be less than 40% with greater than 30% of sperm cells in a sample demonstrating proper motility. An estimated 40 to 90% of male infertility is due to deficient sperm production of indefinable origin (Sinclair, 2000). A large proportion of infertile men fail to impregnate their female counterpart because of lack of sperm (azoospermia) or too little sperm (oligozoospermia); infertility may also be due to abnormal sperm morphology (tetratozoospermia) and insufficient sperm motility (athenozoospermia) (Feng, 2003). A study recently carried out on the sperm characteristics of infertile males at the University College Hospital, Ibadan, Nigeria showed that abnormal semen quality remains a significant contributor to overall infertility with athenozoospermia being the most common seminal quality abnormality (Adeniji et al., 2003). A similar study that was done at the Nnamdi Azikiwe University Teaching Hospital located in South-east Nigeria showed that oligozoospermia (35.9%) and athenozoospermia (32.3%) were the most common aetiological factors responsible for male infertility (Ikechebelu et al., 2003). There are evidences to show that sperm counts have been declining over the last 50 years, with a consequent increase in male infertility. Carlsen et al. (1993) analyzed a total of sixty-one studies from 1938- 1991. The study included 14,947 men and they found that there was a significant decline in mean sperm density from 113 million/ml in 1940 to 66million/ml in 1990 ($P<0.0001$). The seminal volume was also observed to have decreased from an average of 3 - 4 to 2.75 ml ($P = 0.027$). This shows a 20% drop in volume and 58% decline in sperm production in the last 50 years. There are various factors that have been reported to be responsible for this increase in male fertility. Therefore, in this review the different factors that are responsible for male

Abbreviations: **DES**, Diethylstilbestrol; **PCBs**, polychlorinated biphenyls; **DDT**, dichlorodiphenyltrichloroethane; **ROS**, reactive oxygen species, **FSH**, follicle-stimulating hormone; **LH**, luteinizing hormone; **GnRH**, gonadotropin releasing hormone; **hCG**, human chorionic gonadotropin; **HUS**, hemolytic uremic syndrome.

infertility are presented.

ESTROGENS

Estrogen and its derivatives and their synthetic analogs (diethylstilbestrol) are widely used in the livestock, poultry, and dairy industries. Increased exposure to estrogens is thought to be responsible for not only prenatal testicular damage, but may also contribute to post-natal depression of testicular function and spermatogenesis. Exogenous estrogens impact fetal development by inhibiting the development of Sertoli cells, which determine the lifelong capacity for sperm production and men wishing to improve their fertility and sperm quality probably should avoid hormone-containing dairy products and meats and opt instead for organic or hormone-free foods (Sinclair, 2000). Diethylstilbestrol (DES) which was prescribed to millions of pregnant women between 1945 and 1971 resulted in male offsprings from those women having a higher incidence of developmental problems of the reproductive tract, as well as diminished sperm volume and sperm count (Palan and Naz, 1996).

Phytoestrogens (reported in soy beans and many commonly-used pesticides, such as organochloride compounds) have estrogenic effects within the body. Chemicals such as dioxin and dichlorodiphenyltrichloroethane (DDT), phthalates and polychlorinated biphenyls (PCBs) are known to interfere with spermatogenesis. One study which examined the effect of DDT on male rat sexual development found that low levels of DDT caused degeneration in sperm production, a decrease in the total number of sperm, and a reduced number of Leydig cells. The authors hypothesized that DDT acts as a hormonal disrupter, damaging the seminiferous epithelium and lowering local testosterone levels (Krause et al., 1975).

INFECTION

Infections in the male genito-urinary tract including infections of the epididymis, seminal vesicles, prostate, bladder and urethra are thought to play a major role in many cases of infertility (Purvis and Christiansen, 1993) The exact extent of the role they play is largely unknown because of the lack of suitable diagnostic criteria coupled with the asymptomatic nature of many infections. The presence of antisperm antibodies is considered to be a good indicator of a chronic infection in the absence of other clinical findings. There are a wide number of bacteria, viruses, and other organisms which can infect the male genito-urinary system. Chlamydia is now recognized as the most common as well as the most critical of infections in the male genitourinary tract (Purvis and Christiansen, 1993). Chlamydia is considered a sexually transmitted disease. In men, chlamydia is the major cause of acute non-bacterial prostatitis and urethritis. Typically, the symptoms will be pain or burning sensations upon urination or ejaculation. More important is chlamydia infection of the epididymis and vas deferens. The resultant damage to these organs parallels the tubal damage in women; scarring and blockage can occur. During an acute chlamydia infection, antibiotics are essential for its treatment. Chlamydia is sensitive to tetracyclines and erythromycin. Unfortunately, because chlamydia lives within human cells, it may be difficult to totally eradicate the organism with antibiotics alone. While acute chlamydial infections are usually associated with severe pain, chronic infections of the urethra, seminal vesicles, or prostate can go on with little or no symptoms. It is estimated that 28 to 71% of infertile men have evidence of a chlamydial infection (Purvis and Christiansen, 1993).

HEAVY METALS

Lead was the first metal that was demonstrated to have detrimental effect on male fertility. Analysis of sperm count in lead workers showed a decreased sperm count as well as decreased motility and lifespan of sperm, in direct relation to the level of lead in the blood (Xuezhi et al., 1992). Telisman et al. (2000) observed that moderate exposure to lead (blood lead <400 µg/l) and cadmium (blood cadmium <10 µg/l) can significantly reduce semen quality. High concentrations of hexavalent chromium also caused testicular atrophy and decrease in sperm count. In human studies, welders were observed to be exposed to significant amount of chromium and they have been found to have diminished sperm quality (Mortensen, 1988). Exposure to copper has been linked to oligo-, tetrato- and asthenozoospermia (Lahdetie, 1995).

Zinc is perhaps the most critical trace mineral for male sexual function. It is involved in virtually every aspect of male reproduction including the hormone metabolism, sperm formation, and sperm motility (Prasad, 1988). Among many other things, zinc deficiency is characterized by decreased testosterone levels and sperm counts. Zinc levels are typically much lower in infertile men with low sperm counts indicating that a low zinc status may be a contributing factor to infertility.

CIGARETTE SMOKING

Cigarette smoking has been associated with decreased sperm count, alterations in motility, and an overall increase in the number of abnormal sperm (Kulikauskas et al., 1985). A study designed to evaluate seminal zinc levels in smokers and non-smokers found that although smokers did not have significantly lower zinc levels than non-smokers, seminal cadmium levels were significantly increased, especially in those smoking more than one

pack per day (Oldereid et al., 1994). Experimental evidence also suggests that nicotine can alter the function of the hypothalamic-pituitary axis, affecting growth hormone, cortisol, vasopressin, and oxytocin release, which then inhibits the release of luteinizing hormone (LH) and prolactin (Weisberg, 1985). Cigarette smokers were also shown to have higher levels of circulating estradiol and decreased levels of LH, follicle-stimulating hormone (FSH), and prolactin than non-smokers, all of which can negatively impact spermatogenesis. Smokers with low prolactin levels also demonstrated defects in sperm motility (Ochedalski et al., 1994).

NUTRITION

It has been suggested that the polyunsaturated fatty acid, particularly omega-3 fatty acids like docosahexanoic acid should be increased in the diet of males, because they are the major determinant of sperm membrane fluidity (Sinclair, 2000). However, saturated fats, hydrogenated oils, trans-fatty acids, cotton seed oil, coconut and palm oil should be avoided.

Coconut and palm oils are primarily saturated fat while cotton seed contain toxic residues, due to the high levels of gossypol, a substance known to inhibit sperm function. Gossypol is being investigated as the "male birth control pill." Its use as an anti-fertility agent began after studies demonstrated that men who had used crude cotton seed oil as their cooking oil were shown to have low sperm counts followed by total testicular failure (Weller et al., 1985). Excessive consumption of saturated fats combined with inadequate intake of essential fatty acids will change the fatty acid composition of the sperm membranes thus decreasing fluidity and interfering with sperm motility. While the intake of saturated and hydrogenated fats must be eliminated, the intake of polyunsaturated oils should be increased. These oils function in all aspects of sexual function including sperm formation and activity.

SCROTAL TEMPERATURE

The scrotal sac normally keeps the testes at a temperature between 34 and 36°C (Wyngaarden et al., 1992). At temperatures above 36°C, sperm production is greatly inhibited or stopped completely. Typically, the mean scrotal temperature of infertile men is significantly higher than that of fertile men. Active production of sperm requires a temperature of about 3 - 4°C lower than the normal body temperature. This fact is supported by the decreased sperm count seen in pathologies such as varicocele and cryptorchidism, as well as in cases of prolonged sauna exposure and in paralysed patients restricted to wheelchairs (Mieusset et al., 1987; Brindley, 1982). Impairment of spermatogenesis was found to be very high in professional drivers (Thonneau et al., 1996).

RADIATION

The effect of ionizing radiation on male fertility has been reported. Some United States prisoners volunteered to be subjected to x-rays of their testicles in a study that aimed to determine the effect of radiation on spermatogenesis (Clifton and Bremner, 1983). The result showed that a dose of 0.11 Gy caused significant suppression of sperm count, and that radiation of 3-5 Gy led to permanent sterility. It was also reported that the sperm parameters of men who worked in the clean-up of Chernobyl nuclear disaster, were significantly reduced by exposure to more than100 mSv (Cheburkov and Cheburkova, 1993).

REACTIVE OXYGEN SPECIES (ROS)

ROS have a negative effect on sperm parameters. The sperm plasma membrane is very sensitive to the effect of ROS since it contains abundant unsaturated fatty acids. These unsaturated fatty acids create fluidity which is necessary for sperm motility and membrane fusion events such as the acrosome reaction and sperm-egg interaction. However, the unsaturated nature of these molecules predisposes them to ROS attack and ongoing lipid peroxidation throughout the sperm plasma membrane. An increase in the seminal ROS level has been reported in 40% of infertile men (Lewis et al., 1997). Though the antioxidant defense system is active in the semen, its activity is limited as the amount of cytoplasm of the sperm cell is low (Lewis et al., 1997). The presence of high ROS levels in the semen implies an imbalance between ROS production and the antioxidant system. Increased ROS levels can lead to damage with subsequent sperm dysfunction or cell death. These free radical or oxidative damage to sperm is thought to be responsible for many cases of idiopathic oligospermia (Aitken, 1989). Three factors combine to render sperm cells particularly susceptible to free radical damage: (1) A high membrane concentration of polyunsaturated fatty acids; (2) active generation of free radicals and; (3) a lack of defensive enzymes. All of these factors combine to make the health of the sperm critically dependent upon antioxidants. Although most free radicals are produced during normal metabolic processes, the environment contributes greatly to the free radical load. Men exposed to increased levels of sources of free radicals are much more likely to have abnormal sperm and sperm counts (Aitken, 1989; Purvis and Christiansen, 1992).

SPERM ANTIBODIES

The discovery of an immune factor in male infertility was first reported independently by Wilson (1954) and Rumke (1954). It is now well established that men and women

can make antibodies against human spermatozoa and that the immune state may interfere with reproductive success (Jones, 1980; Clarke et al., 1995). Sperm antibodies have been demonstrated in infertile couples (Rumke and Hekman, 1977). There are limited numbers of antigens that are capable of inducing antibodies with antifertility effect. These antigens occur all over the sperm surface. Sperm antibodies may interfere with reproductive function in a variety of ways at different levels, depending on where the antibody is found and where the corresponding antigen is located on the sperm surface (Mathur *et al*., 1986).

THERAPEUTIC DRUGS

Primary infertility may result from the use of various drugs. This phenomenon may be the result of an effect on the hypothalamic-pituitary-gonadal axis or a direct toxic effect on the gonads. Some of the drugs are antineoplastic agents (cyclophosphamide, chlorambucil, busulphan, and methotrexate), glucocorticosteroids, hormonal steroids (diethylstilbestrol, medroxyprogesterone acetate, estrogen, and the constituents of oral contraceptives), antibiotics (sulfasalazine and cotrimoxazole), thyroid supplements, spironolactone, cimetidine, colchicine, marijuana, opiates, and neuroleptic agents (Buchanan and Davis, 1984). Phenothiazines such as chlorpromazine and thioridazine, are commonly used to treat schizophrenia and are known to cause hyperprolactinaemia which induces hypospermatogenesis, impotence and loss of libido in men (Petty, 1999) and decreased sperm function in male rats (Raji et al., 2005a).

NIFEDIPINE-ASSOCIATED INFERTILITY

Clinical nifedipine-associated infertility has been reported. The acrosome reaction is a complex calcium-dependent process (Fraser, 1993). Premature spontaneous acrosome reaction prior to reaching the oocyte, may lead to early sperm cell death. On the other hand, the inability of sperm to undergo stimulated acrosome reaction in response to oocyte investments and/or follicular fluid may lead to the failure of sperm to fertilize the ovum. It has recently been demonstrated that nifedipine, a calcium channel blocker, has the capability of blocking acrosome reaction (Fraser and McIntyre, 1989). A group of men taking nifedipine for hypertension were found to have reversible disordered expression of head-directed mannose-ligand receptors and low rates of acrosome reaction during capacitating conditions. The laboratory was also able to reproduce these findings *in vitro* by introducing nifedipine in the medium of sperm from normal donors (Benoff et al., 1994). Following cessation of the drug, the acrosome reaction status returned to normal and subsequently, pregnancy was achieved (Hershlag et al., 1995).

ANTI-BACTERIAL DRUGS

Antibiotic therapy has been shown to significantly affect spermatogenesis and seminal parameters in both human and animal models. This has been shown with the use of nitrofurantoin (Nelson and Bunge, 1957) and furacin (Paul et al., 1954). Sulfasalazine, commonly used in the treatment of inflammatory bowel disease, has been demonsrated to cause oligospermia and poor sperm motility and is well known to decrease seminal quality (Levi et al., 1979). Tetracycline derivatives, specifically tetracycline hydrochloride, have been shown to cause decreased spermatogenic index (Kushniruk, 1976). Other antibiotics which have been studied and found to affect male fertility negatively include antibiotics in the macrolide group (erythromycin, spiramycin and neomycin) (Timmermans, 1974). Tylosin was reported to inhibit steroidogenesis in mouse (Meisel et al., 1993), while Yildiz et al. (2004) reported that it does not affect gonadotropin releasing hormone (GnRH)-induced luteinizing hormone (LH) secretion in rams.

Antibiotics in the penicillin group (penicillin-G, ampicillin and dicloxacillin) have been implicated in causing spermatogenic arrest (Timmermans, 1974). Ampicillin has been shown to cause significant decrease in fertility capacity and motility of chicken spermatozoa (Wilcox and Shorb, 1958). Similarly dicloxacillin was reported to decrease sperm motility in the bull (Berndtson and Foote, 1976). Raji et al. (2006) showed that ampicillin and cloxacillin caused significant reduction in the weights of testes, epididymides, seminal vesicle and prostate glands. They also found a significant decrease in sperm counts, motility, viability and morphologically abnormal spermatozoa in male rats. Aminoglycosides (gentamycin and neomycin) have been observed to alter testicular functions (Yunda and Kushniruk, 1973).

ANTI-MALARIA DRUGS

Many antimalaria drugs have been implicated in male infertility. For instance chloroquine, quinine and quinacrine have been reported to inhibit Leydig cell steroidogenesis and fertility in male (Sairam, 1978). Chloroquine is an aminoquinoline commonly used in the tropics to treat malaria (Nduka and Dada, 1984). Chloroquine is a lysomotropic agent which inhibits the degradation of internalized human chorionic gonadotropin (hCG) in Leydig (Ascoli and Puett, 1978) and luteal cells (Menon and Rajendra, 1982). It has been shown to have varied effects on male reproductive functions including fertility reduction in male rats (Vawva and Saade, 1987). Chloroquine was shown to inhibit testosterone secretion in hCG-stimulated testis of pubertal rats (Nduka and Dada, 1984).

Chloroquine was also reported to reduce sperm motility and hence fertility by reduction in the average number of fetuses of cohabited females (Adeeko and Dada, 1998).

Okanlawon and Ashiru (1998) showed that in chloroquine treated rats, there was disruption of spermatogenesis, which was accompanied by a decline in serum concentration of testosterone in the rats. Pyrimethamine, a prophylactic antimalarial drug has been shown to cause spermatogenic arrest and male infertility in mice (Trager and Polonsky, 1981). Artemether is another antimalarial drug, which is used to treat all forms of malaria due to *Plasmodium falciparum*, *Plasmodium ovale* and *Plasmodium malariae* (Taylor et al., 1993). It was observed to reduce sperm motility, viability, sperm count and serum testosterone level (Raji et al., 2005b). Quinine ($C_{20}H_{24}N_2O_2$) is a natural white crystalline alkaloid having antipyretic, anti-malarial and analgesic properties and a bitter taste.

It is a drug which is made from the bark of the Cinchona tree, a stereoisomer of quinidine and it is presently the mainstay in the treatment of severe malaria and nocturnal leg cramps (Osinubi et al., 2005). In the past, Cinchona bark was prepared by grinding it to a fine powder, and mixing it with water or wine. Currently however, quinine is generally taken in tablet form, but it can also be taken intravenously by injection. Nowadays, quinine is rarely employed for the treatment of malaria, except for a severe acute form known as falciparum malaria. It is however commonly taken to relieve night-time leg cramps (Upfal, 1991). When used in the suppression of malaria, the usual dosage range is 300 to 600 mg daily. For the treatment of malaria, the dosage range is 1.2 to 2.0 g daily, in divided doses (Medicines Commission, 1980a and b). Excessive doses of quinine can lead to "cinchoism", which is characterized by ringing in the ears, temporary deafness, blurred vision, nausea and abdominal upset. In severe cases, it may even lead to circulatory collapse, kidney failure and coma (Upfal, 1991).

Borovoskaya et al. (2000) observed that a single injection of quinine in a maximum tolerable dose to BALB/c mouse caused morphological changes in the testes and suppressed spermatogenesis. They also found that the gonocytes in all layers of the spermatogenic epithelium, intestinal endocrinocytes and sustenocytes proved to be sensitive to the toxic effect of quinine. Osinubi et al. (2005) also reported that quinine was toxic to testicular gonocytes and the seminiferous tubules of rats. The spermatozoa of mice treated with quinine showed flagellar angulation, which compromises motility, and the spermatozoa are unable to enter the oviduct.

This defect is due to the impaired development of the volume regulatory mechanisms of spermatozoa, normally acquired in the initial segment, as the same flagellar angulation can be induced in normal caput epididymidis spermatozoa by incubation in media or in normal mature spermatozoa from cauda epididymides by volume-sensitive ion channel blocker quinine. Moreover, the angulation can be released by demembranation (Yeung et al., 1999; 2000; 2002). Quinine was also reported to inhibit Leydig cell steriodogenesis and fertility in males (Sairam, 1978).

Crum and Gable (2000) reported the 15th case of quinine-induced hemolytic-uremic syndrome (HUS) in the medical literature. The likely mechanism by which quinine induces HUS is via quinine-dependent antibodies to blood cellular constituents. These antibodies likely cause endothelial damage and the resultant nephropathy, microangiopathic hemolytic anemia, and thrombocytopenia that defines hemolytic uremic syndrome (HUS).

SOME MEDICINAL PLANTS IMPLICATED IN MALE INFERTILITY

Azadirachta indica

Administration of the leaf extract of *A. indica* affects the structure and function of testis and spermatozoa in male rats (Shaikh et al., 1993). It was observed by Raji et al. (2003), that the ethanolic extract of the bark of *A. indica* given to rats by the intraperitoneal route for 10 weeks caused dose dependent decrease in weights of testis, epididymis and seminal vesicle. *A. indica* alters sperm count, morphology and viability and causes dose-dependent reduction in serum testosterone and LH in rats. Most of these changes were however reversible.

Embelia ribes

Embelin (2,5- dihydroxy –3- undicyl-1,4-benzoquinone) isolated from *E. ribes* berries showed spermicidal activity by inhibition of sperm count (Parandare et al., 1979). The compound is believed to have anti- androgenic properties.

Abrus precatorius

Dose dependent reductions in testicular weight, sperm count and degeneraton in later stages of spermatogenesis were found in the testis of rats treated with steroidal fraction of *A. precatorius* seeds (Kulsheshtha and Mathur, 1990).

Quassia amara

Raji and Bolarinwa (1997) observed that the crude methanol extract of the stem wood of *Q. amara* significantly caused a reduction in the weight of testis, epididymis and seminal vesicle but an increase in that of the anterior pituitary gland. Epididymal sperm counts, serum levels of testosterone, LH and FSH were significantly reduced when the rats were treated with the extract. They were also able to isolate two compounds (quassin and 2-methoxycanthin-6-one) from *Q. amara.*

Quassin produced similar biological actions as the crude extract while 2-methoxycanthin-6-one had no antifertility effect. Similar observations of anti-fertility activities of *Q. amara* were reported by Njar et al. (1995) and Parveen et al. (2003).

Carica papaya

Chinoy and George (1983) observed that short term administration of an aqueous extract of *C. papaya* seed manifested an androgen deprived effect on the target organs and thereby caused anti-fertility effect in adult male albino rats. The complete loss of fertility was attributed to a decline in sperm motility and alteration in their morphology as well as reduced contractile response of the vas deferens. They also observed that androgen deprived effect of the extract led to slight alteration in the histo-architecture and weight of reproductive organs, mainly the cauda and distal vas deferens. It was also observed that an oral dose of crude ripe pawpaw (*C. papaya*) seed caused degeneration of the germinal epithelium cell in male albino rats (Udoh and Kehinde, 1999). The chloroform extract of *C. papaya* seed 50 mg/kg/day was administered orally for 360 days to male langur monkeys. The extract decreased the sperm concentration and azoospermia was observed after 90 days of treatment. Treatment withdrawal resulted in gradual recovery and 150 days later, all parameters reverted to nearly the pretreatment values. It was concluded that *C. papaya* seed extract may selectively act on developing germ cells, possibly mediated via Sertoli cells, leading to azoospermia (Lohiya et al., 2002).

Solanum xanthocarpum

Solasodine, a steroidal alkaloid of *S. xanthocarpum,* caused disruptive changes in the acrosomal membrane of sperm and arrest of spermatozoa motility (Kanwar et al.,1988).

Vinca rosea

V. rosea leaf extract has been shown to be anti-spermatogenic as well as anti-androgenic in male rat (Muragavel and Akbarsha, 1991). Vincristine, an indole alkaloid obtained from *V. rosea* caused regression of the seminal vesicle and prostate gland and decreased secretory activity at a dose of 20 µg for 15 days in male rats (Akbarsha et al., 1995).

Alstonia bonei

A. bonei is a tropical plant reputed in traditional medicine to have anti-malarial, anti-pyretic, anti-inflammatory and analgesic properties (Ojewole, 1984; Olajide et al., 2000). Raji et al. (2004) reported that oral administration of 50 and 200 mg/kg b.w/animal/day of the extract for 1, 2, 4, and 12 weeks caused duration and dose-dependent changes in the body and organ weights and sperm characteristics. Sperm viability, motility and counts were significantly reduced ($P < 0.05$) in rats treated for 2 and 4 weeks. Only sperm viability was reduced in rats treated for 1 week. However rats treated for 12 weeks had normal sperm motility, viability and counts. In addition, they had normal serum testosterone concentration and fertility. Fertility was zero in rats that were treated for 2 weeks. Visible lesions in the seminiferous tubular cyto-architecture were observed in the histological sections of the testes from the treated rats prepared at the end of the study period. Normal sperm characteristics were however, restored in rats that were allowed a 4-week recovery period.

Ocimum sanctum

Treatment of albino rats with a benzene extract of *O. sanctum* leaves (250 mg/kg body weight) for 48 days decreased total sperm count, sperm motility, and forward velocity. The percentage of abnormal sperm increased in the caudal epididymal fluid, and the fructose content decreased in the caudal plasma of the epididymis and the seminal vesicles. The results suggest that such effects are due to androgen deprivation, caused by the anti-androgenic property of *O. sanctum* leaves. The effect was reversible because all parameters returned to normal, 2 weeks after the withdrawal of treatment (Ahmed et al., 2002).

Malvaviscus conzattii

Chronic administration of *M. conzattii* flower extract at a dose level of 800 mg/kg b.w. for 30 consecutive days in male rats significantly reduced sperm counts and motility together with histological changes in the testes. Mating with these treated animals three weeks following the drug schedule proved to be consistently infertile (Pakrashi et al. 1985).

Tripterygium wilfordi

A multiglycoside extract of *T. wilfordii* caused a reduction in sperm motility and concentration in males (Quain, 1987). A series of diterpene epoxides have been successfully extracted from the root of the plant. One triptolide was chosen for further pharmacological studies and was found to induce complete infertility in male rats acting primarily on epididymal sperm with minimal effect on the testis (Lue et al., 1998).

Calotropis procera

This plant is popularly referred to as giant milk weed and it was reported to have alkaloids, flavonoids and cardiac glycosides as its main constituents (Hussein et al., 1994). It is used to treat headache, painfull swellings and carious tooth (Iwu, 1993). It was found to decrease testicular weight and it caused testicular degenerative changes (Akinloye et al., 2002).

Cnestis ferruginea

The methanolic and chromatographic fractions of *Cnestis ferruginea* have reversible antifertility effects. The reproductive effects may be due to quinolizidine alkaloid that was characterized from the purified fractions (Olayemi, 2007).

Gossypol

Gossypol is a phenolic compound isolated from cotton seeds and was considered as a drug for male contraceptive use after clinical trials in China (Prasad and Diczfalusy, 1982). In gossypol induced sterility, there was degeneration of spermatids, spermatocytes and germinal cell (Saksena and Salmonsen, 1986). There was however, evidence of animal and human toxicity and high incidence of irreversible testicular damage (Waites, 1999).

CONCLUSION

This review has shown that there are many factors that are responsible for male infertility. The factors responsible for male infertility are in-exhaustible and as such, it is critical that these factors are considered in the treatment of male infertility. More worrisome are the factors that appear “safe” such as, medicinal plants. The use of medicinal plants is on the increase but is also responsible for male infertility. It is therefore highly pertinent that caution should be applied especially with high dosage treatment regime with medicinal plants in men.

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