



Arch. Bas. App. Med.11 (2023):1 -12

www.archivesbamui.com

www.ojshostng.com/index.php/abam

Research Article

Recent advances in the treatment and management of oligospermia in humans

*Ibitoye B.O.¹, Ekpe E.A.¹, Olaniyan O.T.², Ibitoye F.O.³, Bashir F.O.⁴, Femi-Akinlosotu O.⁵

¹Department of Anatomy, Ekiti State University, Ado Ekiti, Nigeria

²Laboratory for Reproductive Biology and Developmental Programming, Department of Physiology, Rhema University, Aba, Nigeria.

³Department of Science Laboratory Technology, Rufus Giwa polytechnic, Owo, Ondo State, Nigeria

⁴Omega Golden Fertility, Plot 8 Tunde Oyerinde Close, Peninsula Estate Ajiwe Ajah, Lagos, Nigeria

⁵Department of Anatomy, University of Ibadan, Ibadan, Nigeria

Accepted: 18 July, 2023

Abstract

Male infertility is frequently characterized by low sperm count, all of which relate to semen having a low concentration of sperm. The shape and motility of the sperm are frequently noticeably aberrant in semen with a lower sperm concentration. Oligospermia is a clinical condition diagnosed via laboratory analysis of a semen spermiogram based on the WHO benchmark for normal sperm concentration. Male infertility represents just under half of the cases of infertility, and most of it is caused by oligospermia. Though assisted reproductive technology is most commonly used for couples with this medical condition, drug treatment is a better option. Treatment for oligospermia depends on the underlying causes, however the majority of instances are idiopathic, and a number of medications have been shown to be successful in treating it. This review article is to outline various drugs and plants that have been recently found to be very effective in the treatment and management of oligospermia in humans.

Key Words: Male infertility, oligospermia, semen, treatment, drug, plant extract

INTRODUCTION

Oligozoospermia is a disorder where sperm concentration is below the lower reference limit of 15 million sperm/mL of ejaculate. Oligozoospermia can be further classified as mild (between 10 and 15 million sperm/mL), moderate oligozoospermia (between 5 and 10 million sperm/mL), and severe oligozoospermia (less than 5 million sperm/mL; Rondanino and Rives, 2020). Oligozoospermia diagnosing can be challenging, as several conditions are recognized to result in oligozoospermia. Therefore, a formal and precise diagnosis can be relevant in giving patients a reason for their sterility and decreasing confusion, fear, and stigma (Rondanino and Rives, 2020).

Oligospermia is a decrease in the sperm concentration in semen below 15 million sperm per milliliter (WHO, 2010). Oligospermia is a defect in sperm production and may be due to surgically correctable causes like varicocele, exposure to thermal or chemical environmental factors suppressing spermatogenesis, hormonal factors, intrinsic testicular defect or idiopathic. (WHO, 2010). Specific treatment of oligospermia requires proper evaluation of the patient to identify its cause. Oligospermia may be multi-factorial and the

patients are informed that smoking, exposure to heat or chemicals and wearing tight clothes may be additional causes of oligospermia. Patients are advised to modify their life style and avoid such factors that inversely affect the process of normal spermatogenesis. (Alayman, 2018).

Classification of Oligospermia

According to the latest World Health Organization guidelines (2021, oligospermia is due to a sperm concentration of less than 15 million/ml of seminal fluid (Organization & others, 2021). Anything below that is deemed low, and oligospermia is diagnosed.

- Mild oligospermia is 10 to 15 million sperm/mL.
- Moderate oligospermia is considered 5 to 10 million sperm/mL.
- Severe oligospermia is diagnosed when sperm counts fall between 0 and 5 million sperm/mL.

Causes of oligozoospermia

The causes of oligospermia are categorized into three categories: pre-testicular, testicular, and post-testicular. Changes in these hormones; follicle stimulating hormone and luteinizing hormone (FSH and LH), anabolic steroids, drugs,

nicotine, alcohol, and stress are all examples of pre-testicular factors that are linked to sperm production indirectly. This can be resolved by adopting a healthier way of life. Testicular causes are those that impact the function of the testes in some way. Cryptorchidism, Hydrocele varicocele, orchitis, trauma, and genetic abnormalities are some of them. Obstructive oligospermia is caused by the post-testicular and Iatrogenic, congenital, infection, and inflammation are all possibilities (Gonçalves *et al.*, 2017). The luteinizing and testosterone levels are normal, irrespective of the sperm count, but follicle stimulating hormone levels were inversely connected to the spermatozoa concentration, in order to understand the reasons for idiopathic oligospermia in humans (Fauser *et al.*, 1990).

There have been several drug trials, especially in idiopathic oligospermia, that will be effective and also inexpensive and safe. In males with idiopathic oligospermia, long-term treatment with oral lisinopril was found to improve sperm quantity and quality, as well as improve fertility in about half of those treated (Lazzaroni *et al.* 2022). Clomiphene, gonadotropins, bromocriptine, L-thyroxin, vitamin E, and vitamin B12 have also been tested, albeit with mixed success (Mbah *et al.*, 2012). Treatment of oligospermia with the amino acid arginine was attempted, as was the therapeutic effect of natural vitamin E (Vit E) on oligospermia and asthenospermia in infertile males. However, treatment with bromocriptine did not produce a favorable response (Arab *et al.*, 2021).

In Cameroon, Central Africa, and other low- and middle-income nations, medicinal plants have been shown to play significant roles in the management of reproductive healthcare due to the lack of a suitable medicine for the treatment of oligospermia as well as other considerations. (Malviya *et al.*, 2016). Approximately 80% of the African population uses traditional methods, mostly because of their easy accessibility and affordability (Nsagha *et al.*, 2020). Alternative medicine boosts sperm volume, count, and motility in idiopathic oligozoospermia patients, according to a study (Terai *et al.*, 2020). When compared to placebo granules, the fruits of Gokshura (*Tribulus terrestris*. Linn) have demonstrated superior efficacy in the treatment of oligospermia in human investigations (Rosenthal *et al.*, 2022). At least in a subset of oligospermic males, antioxidant therapy based on micronutrient supplementation can enhance sperm count (Tsampoukas *et al.*, 2021). Antioxidants can protect sperm from the negative effects of free radicals. Reducing oxidative stress can improve the likelihood of natural or assisted reproductive technology (ART) fertility (Ribas-Maynou and Yeste, 2020). The effects of a combination of herbs (onion, ginger, basil, cinnamon, orange peel, yellow and red watermelon seeds, and carrot seed) on catalase levels in the sperm of males with oligospermia were studied (Ainehchi *et al.*, 2019). Propolis (a folklore treatment) orally modifies the harmful effects of taxol by improving semen quality, reducing oxidative stress, preventing DNA damage, and maintaining cell energy (Martins *et al.*, 2021). Other treatments, including as clomiphene citrate, tamoxifen, recombinant FSH, zinc, selenium, and L-carnitine, have had mixed results (Ring *et al.*, 2016).

Although the majority of cases are idiopathic, male infertility due to oligospermia is surprisingly prevalent. People who come down with the condition can be caused by a wide range of illnesses, making it difficult to assess. Unfortunately, 60% to 75% of men will not acquire a conclusive diagnosis to

explain their oligozoospermia even after a complete investigation (Punab *et al.*, 2017). However, if a diagnosis can be made, it is extremely helpful in deciding proper treatment for many individuals, as detailed here. A professional diagnosis can also help patients understand the reason for their infertility, which can help them feel less confused, guilty, and embarrassed (Choy & Amory, 2020). Oligospermia can be caused by partial or complete occlusion of the tubes that carry semen from the testis. Infection, inflammatory, or congenital causes of blockage are all possibilities. Oligospermia could have an idiopathic cause (Tournaye *et al.*, 2017).

Hypothalamic dysfunction

The most frequent type of congenital disease is GnRH secretion deficit. Different genetic disorders can cause different forms of anosmic presentation, Kallmann syndrome, and normosmic presentation, all of which can be acquired (Cangiano *et al.*, 2021). There are partial forms of the syndrome that allow for some pubertal development or, in rare circumstances, complete pubertal development before hypogonadotropic hypogonadism develops. GnRH deficiency is commonly detected by a lack of sexual maturation throughout puberty (Cangiano *et al.*, 2021).

Gonadotropin-releasing hormone (GnRH), which is normally produced and secreted by the hypothalamus in a pulsatile fashion into the hypothalamo-hypophyseal portal circulation, stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) into the systemic circulation by gonadotroph cells. FSH activates the Sertoli cells within the seminiferous tubules to increase spermatogenesis while LH stimulates the Leydig cells in the testes to synthesize and release testosterone. As a result of the testosterone's partial aromatization into estradiol and the release of inhibin B by activated Sertoli cells, the brain and pituitary receive negative feedback, which reduces the production of LH and FSH, respectively (Anawalt *et al.*, 2017). Many of the endocrine-based etiologies of oligozoospermia are caused by disruption of this highly regulated hormonal axis. Any decrease in gonadotropin secretion, in particular, will interfere with intratesticular testosterone production and spermatogenesis (Choy & Amory, 2020).

Pituitary dysfunction: Gonadotropin secretion can be disrupted or suppressed by a variety of pituitary pathologies, including mass lesions and infiltrative pituitary disease. Pituitary adenomas, craniopharyngiomas, and Rathke's cleft cysts are examples of sellar masses that can have a mass effect on gonadotroph cells, preventing hormone release. The most prevalent type of pituitary adenoma, known as a prolactinoma or prolactin-secreting pituitary adenoma, results in hyperprolactinemia, which inhibits the hypothalamic-pituitary-gonadal axis and results in hypogonadotropic hypogonadism (Samperi *et al.*, 2019). It is recognized that ischemic injuries such pituitary apoplexy and infiltrative diseases of the pituitary including sarcoidosis, hemochromatosis, and Langerhans histiocytosis can lead to hypopituitarism (Javorsky *et al.*, 2021).

Thyroid disease: Male fertility and spermatogenesis can be harmed by both hyperthyroidism and hypothyroidism. A hyperestrogenic condition is facilitated by increased

androstenedione and testosterone aromatization to circulating estrogens in peripheral tissues in hyperthyroidism (Pilny, 2014). Excess thyroid hormone also inhibits Sertoli cell growth, lowering spermatogenic ability (Alahmar *et al.*, 2019). hyperthyroidism can result in considerably elevated sex hormone binding globulin (SHBG) levels, which can impair free and bioavailable blood testosterone levels despite increasing total serum testosterone measurements (La Vignera *et al.*, 2017). It has been demonstrated that hypothyroidism impairs testicular development in the years leading up to puberty (Aiceles., 2016). Primary hypothyroidism also results in a compensatory rise in thyrotropin-releasing hormone release from the hypothalamus. Thyrotropin-releasing hormone causes hyperprolactinemia and hypothalamic suppression by activating lactotroph cells. The pituitary-gonadal axis is a complex relationship between the pituitary and the gonadal glands (Ansari, 2016).

Adrenal dysfunction: The hypothalamic-pituitary-gonadal axis is suppressed by adrenal androgens (Amiri *et al.*, 2018). Congenital adrenal hyperplasia is brought on by an enzyme deficiency in the adrenocortical steroidal synthesis pathway, such as 21-hydroxylase deficiency (Parsa, 2017). Due to this disease, which is brought on by high Adrenocorticotropic Hormone (ACTH) secretion, there is an excess of adrenal androgens produced as well as a shortage of glucocorticoids. Suspicion for this condition is elevated when repressed gonadotropins and normal to higher testosterone levels are observed (Hahner *et al.*, 2021). The presence of high 17-hydroxyprogesterone and androstenedione levels in the blood confirms the diagnosis. Treatment with glucocorticoid replacement can reduce gonadotropin suppression and fertility by suppressing excessive adrenal steroidogenesis (Engels *et al.*, 2018).

Genetic syndromes: The presence of severe oligozoospermia raises the possibility of a hereditary etiology of infertility. The most prevalent chromosomal defect in men is Klinefelter syndrome (KS) (Salzano *et al.*, 2018). One in 500 live newborns may be affected by KS, and azoospermic men are 10 to 15 percent more likely to have the condition (Vander., 2018). While most men with KS are azoospermic, situations of genetic mosaicism might result in oligozoospermia. Male infertility in men with normal karyotypes has been linked genetically to deletions on the long arm of the Y chromosome. In 5% to 10% of azoospermic males and 2% to 5% of severely oligozoospermic, Y chromosomal microdeletions have been discovered (Tournaye *et al.*, 2017). Phenotypic diversity is caused by deletions in specific regions of the AZF locus on the Y chromosome, which affect spermatogenesis differently. For instance, extensive deletions or deletions impacting the AZFa and AZFb regions make it extremely unlikely that surgical sperm retrieval will be successful, so management strategies should be altered accordingly. (Punjani *et al.*, 2020). Finally, male infertility is frequently caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Most CFTR mutations result in congenital bilateral vas deferens absence and azoospermia; nevertheless, men with CFTR mutations with severe oligozoospermia have been reported (Yu *et al.*, 2012). In affected patients, a low-volume, acidic ejaculate is common, indicating the absence of seminal vesicles (Mieusset *et al.*, 2020).

Medications: Many drugs have been shown to have an effect on the hypothalamic-pituitary-testicular axis, which can result in infertility due to oligozoospermia. Long-term opioid medication has endocrine consequences that include suppression of the hypothalamic-pituitary-gonadal axis, which results in hypogonadism, sexual dysfunction, and infertility, due to cessation of hypothalamic pulsatile GnRH release (Blendon, 2018). However, the resulting supraphysiologic androgen levels negatively feedback on the hypothalamic-pituitary-gonadal axis. When testosterone levels are too high, it can aromatize into estradiol, which has negative effects include gynecomastia and a reduction in pituitary gonadotropin secretion (Hammes *et al.*, 2019). Commonly used to treat autoimmune and inflammatory diseases are glucocorticoids. Since glucocorticoids prevent GnRH from being produced and released in the hypothalamus, they have also been associated with hypogonadotropic hypogonadism. With long-term glucocorticoid medication, the inhibition of the gonadal axis becomes increasingly profound. Furthermore, glucocorticoids may prevent Leydig cells from producing testosterone (Xu *et al.*, 2017). Finally, Other medications with the potential to decrease male fertility include cannabis, antipsychotics, 5-reductase inhibitors, and maybe antidepressants from the serotonin-selective reuptake inhibitor class (Akingbade *et al.*, 2017).

Chemotherapy and radiation therapy can damage the seminiferous tubules, resulting in azoospermia or oligozoospermia (Tharakan *et al.*, 2020). Sperm cryopreservation should be routinely offered to patients prior to commencing oncologic treatment as a crucial part of fertility preservation counseling due to the detrimental effects of these medications on fertility (Shankara-Narayana *et al.*, 2019).

Obesity: There is a J-shaped relationship between body mass index and oligozoospermia, with the underweight state being associated with an increased, non-significant risk of low sperm counts and the overweight and obese states being associated with an increased, non-significant risk of low sperm counts, according to a meta-analysis of over 13,000 men looking at the relationship between male infertility and the metabolic syndrome (Hart *et al.*, 2019). However, not all research have found a similar link, indicating data inconsistency and a lack of consensus on this possible relationship (Benammar *et al.*, 2021). Obesity is associated with greater levels of leptin and insulin resistance, which inhibits kisspeptin's ability to activate GnRH neurons in the hypothalamus and lowers gonadotropin output. The production of aromatase, an enzyme that changes testosterone into estrogen, is also increased by increased adiposity, exacerbating androgen deficiency and inhibiting the hypothalamic-pituitary-gonadal axis (Fernandez *et al.*, 2019). Finally, the epigenetic effects of paternal obesity on offspring's health are troubling, with a recent observational study finding significantly greater chances of preterm birth, low birth weight, and neonatal intensive care unit admission in dads with most of the metabolic syndrome's components (Kasman *et al.*, 2020).

Anatomic disorders: Varicoceles are pathological enlargements of the venous pampiniform plexus of the spermatic cord. Between 35 and 40 % of infertile men have

varicoceles, which can lead to issues with spermatogenesis include sloughing of seminiferous tubule germ cells, atrophy of the testicles, and insufficient testosterone levels (Taghizadeh *et al.*, 2017). Numerous hypotheses regarding how varicoceles may contribute to testicular dysfunction have been put forth, including testicular hyperthermia, increased testicular oxidative stress, and reflux of renal and adrenal metabolites that have a toxic effect on spermatogenesis. This debate over association versus causation is still ongoing (Modgil *et al.*, 2016). This group of men includes those with oligozoospermia or azoospermia with an ejaculate volume of less than 1 mL due to the lack of the alkalizing seminal vesicle secretions from the ejaculate, the ductal obstruction may be partial, full, unilateral, or bilateral, and a low pH and decreased fructose concentration in the semen may be found upon analysis. Additionally, spinal cord damage, neurological conditions, diabetes mellitus, surgeries, the use of alpha-antagonists or other medicines that relax the bladder neck might result in retrograde ejaculation (Mehta, 2015).

Testicular injury: Primary testicular failure and hypergonadotropic hypogonadism can develop from any process that causes direct testicular damage. Spermatogenesis can be interrupted if the testicular architecture is compromised. Testicular trauma, torsion, and gonadotoxic exposures are examples of precipitants in this category. The severity of the condition and the possibility of spermatogenic recovery depend on the agent, dose, and length of treatment. Globally, infertility is a serious health issue with Sperm abnormalities as one of the main causes of male infertility. The most common test used to assess male fertility is semen analysis. A laboratory study of a semen spermiogram using the WHO standard for normal sperm concentration is used to diagnose oligospermia. About 50% of recognized infertility factors are male-related factors, and are mainly the result of oligospermia, astenospermia, and teratozoospermia (Alizadeh *et al.*, 2015). It has been classified based on severity and causes, which will ultimately serve as a prognostic factor.

Several means of treatment have been acclaimed, both orthodox and nonorthodox, but none has been accepted as a golden means of treatment due to lack of consistent or significant improvement (Rabinowitz *et al.*, 2021). Treatment of oligospermia is a difficult clinical condition since it is a primary cause of male infertility, which is a significant and global public health issue (Rastrelli *et al.*, 2019). Assisted reproductive technique (ART) measures are sometimes considered as way out but this has a lot of challenges and the choice of ART depends on the degree of severity of oligospermia (Benammar *et al.*, 2021). Testicular atrophy and subfertility can result from infections of the testicles, such as mumps orchitis, which cause seminiferous tubule destruction and parenchymal inflammation (Olaniyan *et al.*, 2020).

Drug/Plant extract for treating oligospermia

Lisinopril: Angiotensin-converting enzyme (ACE) inhibitor lisinopril is effective in treating heart failure, hypertension, and other cardiovascular and renal illnesses. Both angiotensin (Ang) I to Ang II and kinin hydrolysis are blocked by ACE inhibitors, which has cardioprotective benefits (Lopez *et al.*, 2022). Changes in the expression of angiotensin-converting enzyme-1, angiotensin-converting enzyme-2, and angiotensin-converting enzyme-3 may be one of the most

important reasons causing infertility. Additionally, research shows that testicular ACE1 is exclusively expressed in mature spermatozoa, spermatid heads, and residual bodies, and is only present in the cytoplasm of epididymal sperm (Olaniyan *et al.*, 2020). Testicular angiotensin converting enzyme (tACE1) is known to play an important role in capacitation, according to numerous research. Sperm motility during epididymal transit is decreased by ACE1 through promoting the translocation of ADAM3. Studies have demonstrated that peptidase-inactivated mutants of ACE1 and PI-PLC can restore the defective ability of Ace1-knockout sperm to connect to eggs, indicating that tACE1 plays a crucial role in fertilization through this activity. In the male reproductive system, adult Leydig cells in the testis particularly express ACE2. RAS-blocking medications have been shown to be useful against a number of metabolic syndrome symptoms, indirectly enhancing reproductive health (Eskandari *et al.*, 2020).

Ramipril: Angiotensin Converting Enzyme Inhibitor (ACEI) ramipril is a drug used to treat high blood pressure. Previous research has demonstrated that this family of drugs can increase sperm parameters. Numerous empirical non-specific treatments have been used to enhance their semen quality and fertility. There is very little research on the impact of ramipril on sperm production; nevertheless, in certain studies, ramipril treatments did not show any significant differences from the control group in terms of sperm production, testicular morphology, or radioimmunoassay of serum testosterone levels (Aykan *et al.*, 2020).

Clomiphene: A non-steroidal reproductive medication called clomiphene triggers the release of ovulation-inducing hormones from the pituitary gland (the release of an egg from the ovary). Clomiphene citrate (CC) is a common drug used in reproductive clinics to increase gonadotropin output (Yilmaz *et al.*, 2018). By increasing the blood level of testosterone, clomiphene citrate has also been demonstrated to be useful in the long-term treatment of male hypogonadism. Clomiphene citrate also raises males' levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (FSH). Because of the complexity of hormone interactions, it is difficult to determine if elevating LH and FSH has an immediate impact on male fertility. According to research, clinical investigations examining the effectiveness of using clomiphene citrate for male infertility have shown inconsistent results. Clomiphene citrate might be beneficial to some males while others are not improved clinically (Bridges *et al.*, 2015). Some individuals who use clomiphene citrate may have a lower overall sperm count and this could be due to the dosage as there is no agreement on the ideal dosage of the drug administered. The FDA has not approved clomiphene citrate for treating male infertility (Earl., 2019). It is believed to be superior to testosterone replacement therapy in terms of sperm concentration and the quantity of spermatozoa with progressive motility while promoting testosterone synthesis. It is given subcutaneously in doses of 1,500–3,000 IU, 1-3 times per week (Puia & Pricop, 2022).

Enclomiphene citrate: The trans isomer of clomiphene citrate, an FDA-approved non-steroidal estrogen receptor antagonist used to treat female ovarian dysfunction, is enclomiphene citrate. (Wiehle *et al.*, 2014). Enclomiphene

citrate preserves sperm production while reversing the two symptoms of secondary hypogonadism, low blood total T and low or inappropriately normal LH (Kaminetsky *et al.*, 2013). By boosting levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), enclomiphene citrate enhances serum testosterone levels in cases of androgen deficiency without negatively impacting the semen parameters. (Wheeler *et al.*, 2019).

Anastrozole: In order to increase endogenous testosterone levels and cure male infertility in men with an abnormal testosterone-to-estradiol ratio, anastrozole is employed. The fourth-generation aromatase inhibitor, anastrozole, is non-steroidal and blocks the conversion of testosterone to estradiol. Anastrozole enhances hormonal profiles and semen parameters in hypogonadal, infertile men with body mass index greater than 25 kg/m², and may aid in conception, particularly when administered in conjunction with assisted reproductive techniques. (Aykan *et al.*, 2020). An aromatase inhibitor can be used to treat infertile men who have low serum testosterone-to-estradiol ratios. With treatment, semen parameters increased along with an increase in the testosterone-to-estradiol ratio. The effects of anastrozole and testolactone on hormonal profiles and semen analysis are comparable. For treating men with aberrant testosterone-to-estradiol ratios, anastrozole seems to be at least as successful as testolactone. Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), and the testosterone-to-estradiol ratio (T/E₂) were all significantly elevated after anastrozole (AZ) administration, however E₂ levels were dramatically decreased in comparison to baseline levels (Del Giudice *et al.*, 2020). Additionally, it has been shown to increase sperm production and recovery rates in azoospermic or low sperm count men. Anastrozole, however, had no discernible impact on sperm quantity, motility, or morphology, according to a study (Cohen *et al.*, 2020; Ring *et al.*, 2016).

Human chorionic gonadotropin (HCG): The 145 amino acid beta subunit of human chorionic gonadotropin (hCG) and the 92 amino acid alpha subunit make up the dimer. The luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH) alpha-subunits are identical (TSH). HCG can be used to boost testosterone levels in males who have low testosterone or hypogonadism symptoms (testosterone deficiency). Because it involves two to three injections each week, which most patients would prefer avoid, this medicine is often used as a last option treatment (Fink *et al.*, 2021). According to another study, hCG can increase the chances of successful sperm retrieval in males with non-obstructive azoospermia by increasing testosterone production (Klami *et al.*, 2018). In a survey, 56 men were recruited and they received a weekly injection of 250 g (or around 6,500 IU) of hCG for a period of three to six months. A significant increase in sperm concentration and count was seen after three months of treatment (Kielik *et al.*, 2021).

Coenzyme Q10: Coenzyme Q10 is a chemical that is generated in individual by consuming food or taking as a nutritional supplement. It is not a prescription drug. It's also a potent antioxidant that's been proved to help with a number of

health issues, including male fertility (Tirabassi *et al.*, 2015) It has been proven to improve both sperm integrity and sperm motility in men with defective sperm parameters. Men with pyospermia, or an excess of white blood cells in the sperm, may benefit from coenzyme Q10. It's critical to follow up with semen testing and medical visits to assess the medication's effectiveness (Sharma *et al.*, 2021). In an in vitro study, the quantity of ROS was dramatically decreased when Coq10 was added to human sperm medium. This decrease in ROS lessened cryoprotection-related sperm harm (Nezhad *et al.*, 2021). A case-control study was conducted in the Department of Chemistry and Biochemistry, College of Medicine, Al-Nahrain University, Baghdad, Iraq, 60 cases of male infertility was recruited. By using an enhanced high performance liquid chromatography (HPLC) technology, seminal plasma samples were examined for CoQ10 as well as for malondialdehyde (MDA), a marker of oxidative stress. High levels of seminal plasma CoQ10 are inversely correlated with oxidative stress and directly correlate with healthy semen characteristics (Acton, 2012).

Tamoxifen citrate: Selective estrogen receptor modulators (SERMs), which include tamoxifen, are a poorly researched class of medicines for the treatment of male infertility. When compared to baseline values, SERM significantly increased sperm concentration, total sperm count, serum luteinizing hormone, follicle-stimulating hormone, and total testosterone levels. After three months of treatment, many randomized controlled trials looking at the effectiveness of tamoxifen (20 mg daily) or toremifene plus raloxifene (60 mg daily) in males with oligozoospermia or azoospermia revealed improvements in semen parameters and pregnancy rates. In males with idiopathic oligozoospermia, tamoxifen effectively raises testosterone levels and sperm counts (Dimakopoulou *et al.*, 2021). Tamoxifen citrate enhances spermatogenesis by boosting FSH, Leydig cell sensitivity to LH, and testosterone levels without having an intrinsic oestrogenic action, thus it may be a better choice for male infertility. Double-blind, placebo-controlled, randomized studies are required to assess the findings' (Kadioglu, 2009). Because of tamoxifen's effectiveness on the seminiferous tubules during the early stages of spermatogenesis, previous research revealed that while it had no impact on other semen characteristics including volume, pH, motility, morphology, or viability, it boosted sperm concentration in infertile men with oligozoospermia. (El Meliegy *et al.*, 2018).

Toremifene: Three months of toremifene administration resulted in considerable improvements in sperm count, motility, and morphology. These changes were likely caused by enhanced gonadotropin production and/or a direct toremifene benefit to the testes. The data also point to a greater testicular exocrine (enhanced sperm parameters) response to treatment in men who had successful pregnancies than those who did not. More randomized, placebo-controlled trials should be undertaken to see if this selective estrogen receptor modulator can be used as a first-line treatment in males with oligospermia pyelonephritis (Farmakiotis *et al.*, 2007).

Mesterolone: Mesterolone a synthetic androgen (17 β -hydroxy-1 α -methyl-5 α -androstan-3-one) is effective in patients with sperm counts of 5 to 20 m/ml. This treatment

does not appear to assist those with severe oligospermia (count fewer than 5 million) (Singh., 2013). There is controversy on its effectiveness for treating oligospermia because of its improvement in increasing semen quality, but there has been no detailed study of serum gonadotrophin and testosterone levels during a clinical trial with this drug. Forty subfertile men with oligospermia were treated with Mesterolone and the effect of the drug was a significant decrease in serum testosterone, a pronounced increase in serum LH. The analysis of variance of sperm concentration and motility for the periods before and after treatment, for all the patients, showed no significant difference in the sperm concentration (Varma and Patel, 1988)

L-ergothionein: L-ergothioneine (L-erg) is a naturally occurring 2-thio-imidazole amino acid that is particularly stable in aqueous solution and low molecular weight diet because it does not auto-oxidize at physiological pH. This substance may have important physiological effects on human health, development as well as on the prevention and treatment of disease. It can accumulate in the body at high levels as a result of feeding on mushrooms, beef, pork, etc. (Ayobami *et al.*, 2019). L-erg is only absorbed by humans through a plant-based diet, notably through the intake of edible mushrooms and meat. It was demonstrated by Ayobami *et al.* that L-ergothioneine supplement has protective effects on Cisplatin-induced testicular dysfunction via its antioxidant and cytoprotectant activities in rat. L-ergothioneine supplement considerably reduces these harmful effects of Cisplatin. Thus there need for further studies if patients receiving Cisplatin therapy, may benefit from it as a therapeutic adjuvant to prevent reproductive damage (Ayobami *et al.*, 2019). A study found that adding ergothioneine to semen extenders improved the ram sperm's motility and motion characteristics more than other sperm types (Çoyan *et al.*, 2011).

Polyherbal formulation (PHF): Polyherbal formulation (PHF) is one of herbal amalgams which is a mixture of herbs that is used for various sexual dysfunctions ranging from erectile dysfunction to oligospermia. It has several components like steroid, flavonoid, alkaloid and saponins which all act to restore fertility and effective functioning of male genitalia (Hussain *et al.*, 2018).

Puncture vine (*Tribulus terrestris* L): Puncture vine also known as *Tribulus terrestris* L. (TT) is a member of the Zygophyllaceae family and it is historically known for its role in restoring sexual dysfunction and infertility (Akhtar *et al.*, 2011). In male rats, it is found to improve sexual behavior and enhances sperm production. This effect was also seen in species like rabbit and nonhuman primates. In human, following clinical studies, TT was seen to have the stimulatory effects on the quantity of sperm and increase libido in men (Ahmed *et al.*, 2020). This actions could be due to increase in androgen levels seen following its administration in both human and experimental animals (Ahmed *et al.*, 2020). The active phytochemical in TT is protodioscin which induces the proliferation germinal epithelium by its ability to convert testosterone into dihydrotestosterone (Ahmed *et al.*, 2020).

Red silk-cotton tree (*Bombax ceiba* L.; Malvaceae (L.) Gaertn): *Bombax ceiba* L. is also known as Salmalia

malabarica (DC.) Schott & Endl. and it is called red silk cotton tree. It belongs to family of Bombacaceae Indian silk cotton. It was believed to improve sperm quality, resolved impotency and hydrocele following three day administration of its ethanol extract. Similar finding was seen by ingestion of tonic made from the bark of the tree (Meenakshi *et al.*, 2019).

Malaysian ginseng (*Eurycoma longifolia* - tongkat : *Eurycoma longifolia* Jack. (also known as *Tongkat ali*), Malaysian ginseng or Jack, is a widespread shrub found along the slopes of the Malaysian rainforest's mountainous terrains. It is documented traditionally to enhance sexuality and fertility, as well as an anti-aging tonic and anticancer. A study has implicated presence of its glycoprotein components which are quassinoids as the chemical responsible for this action which has testosterone-boosting and antioxidant characteristics in rats. This was similarly observed in human studies where it increase total testosterone and dihydroepiandrosterone levels in human experiments (Dharvind, 2019). This claim was confirmed in human studies, this was achieved through correction This plant extract was also found to increase serum level of growth hormone and enhanced positive oxidative profile of the body (Tambi, 2010). In rats' the number of germ cells, the rate of spermatozoa production, the height of the germinal epithelium, and the number of Leydig cells were found to increased dramatically after treatment. In addition, in vitro experiment revealed that quassinoid eurycomanone increase local testosterone production by Leydig cells while it decreases estrogen (Chan, 2021).

Fluted pumpkin (*Telfairia occidentalis* Hook.f.): *Telfairia occidentalis* is a tropical vine grown in West Africa as a leaf vegetable and for its edible seeds. The plant is rich in protein, carbohydrate, and minerals such as iron, calcium, potassium, phosphorus, sodium, including antioxidants (vitamins A, C, E), oxalates, saponin, glycosides, flavonoids, alkaloids and resins (Alahmadi, 2020). It has been demonstrated that *Telfairia occidentalis* has a preventive effect against alcohol-induced testicular damage and improves the quality of sperm through increased levels of serum testosterone and luteinizing hormone and better germinal epithelial lining. The effect is dose-dependent (Akang *et al.*, 2011). There was an increase in testosterone, luteinizing hormone, sperm count, sperm motility, and testicular weight as well as an improvement in the secretory capacity of the testes in rats after alcohol-induced testicular damage was treated with 400 mg/kg of the seed oil. The leaf extract increased sperm motility, sperm viability, and sperm count. A similar finding was seen when 400 mg/kg of the seed oil was administered (Akang *et al.*, 2011)

Maca (*Lepidium meyenii* Walp): Maca (*Lepidium meyenii*) is an Andean root that has been consumed for strength and fertility way before written records. A recent study shows that maca's bioactive compounds are capable of improving in vitro fertilization rates by increasing sperm motility and stimulating the activity of acrosomes in order to improve the chances of fertilization (Noh *et al.*, 2020). Maca extract in doses up to 5 g/kg was found to be safe and have an effect on reproductive parameters in rats' studies. Normal men's sperm count and motility improved but blood testosterone and estradiol levels remained unchanged (Tafari *et al.*, 2021).

Velvet bean (*Mucuna pruriens* L.): The commonly used medication in the Ayurvedic and Unani systems of medicine is Velvet bean or *Mucuna pruriens* L. (Fabaceae). According to anecdotal investigations, the medicines made from the seeds are useful in treating male infertility and improving male desire and sexual performance (Rajeshwar *et al.*, 2005). In animal studies using male Guinea pigs, there was increase in testicular weight and testosterone levels, testicular cholesterol levels, testis and epididymis protein levels, and epididymal alkaline phosphatase activity (Mandal *et al.*, 2020). Improvement in semen quality was achieved by modulating steroidogenesis and the hypothalamus in infertile men treated with *M. pruriens*. Increase in testosterone and LH levels were also observed (Divya *et al.*, 2017). It also reduce the reactive oxygen species in the body and enhance antioxidants and ascorbic acid in infertile men's seminal plasma (Divya *et al.*, 2017). Thus there are scientific evidence supporting the efficacy of mucuna as a phytotherapeutic for enhancing serum testosterone concentrations and sperm parameters (Mandal *et al.*, 2020).

Ashwagandha (*Withania somnifera* (L.) Dunal): *Withania somnifera* Solanaceae is commonly known as Ashwagandha in Ayurvedic medicine and the whole part is used for medicine in India. It is a small evergreen shrub with long tuberous roots that belong to the Solanaceae (nightshade) family of plants (Dar *et al.*, 2015). The root of *Withania somnifera* is used as an adaptogen, diuretic, sedative, antioxidant, and aphrodisiac and can be used to treat male infertility (Narinderpal *et al.*, 2013). In human study where a group was given the root extract and other given a placebo, there is improved functionality of male reproductive system and regulation of serum hormonal level, thus effective in treating oligospermia and infertility (Mandlik, 2021). In another study, individuals with oligozoospermia was placed on a 12-week course of ashwagandha root extract, there was significant increase in the spermograms and serum testosterone concentrations (Darbandi *et al.*, 2018). The mechanism of action is by reducing lipid peroxidation, enhance sperm count and motility, and control reproductive hormone levels when consumed orally. However, the molecular processes behind these effects have yet to be discovered (Darbandi *et al.*, 2018).

Black seeds (*Nigella sativa* L., Ranunculaceae): Black seed (*Nigella sativa* L.) has been an important traditional therapy for infertility, which belongs to the family Ranunculaceae (Kamarzaman, 2014). It is one of the common and popular seed widely used medicinally. *Nigella sativa* treatment, increased sperm count in cyclophosphamide-induced testiculotoxicity in rats. The seed has antioxidant qualities that might modulate the germ cell line, as evidenced by the increased number of sperm count after *Nigella sativa* was added to the diet of the experimental animals (Alahmadi, 2020).

Walnut (*Plukenetia conophora*): The plant, *Plukenetia conophora*, often known as African Walnut. One remedy for boosting male fertility is walnut leaf, which is also utilized as alternative to conventional medical practices (Ayodeji and Aliyu, 2018). When walnut oil was administered to Wistar rats, a study found that the testis and epididymis weight, serum

levels of testosterone, luteinizing hormone (LH), and follicle-stimulating hormone all increased significantly. Spermograms also improved (Olaolu *et al.*, 2022). Nitrite-induced oxidative stress, which disrupts spermatogenesis, was mitigated by walnut oil. Analysis revealed that the extract inhibited the activities of arginase, acetyl choline esterase (AChE), and angiotensin-converting enzyme (ACE) in in vitro experiments. (Chijoke *et al.*, 2017). There was improvement in the sperm parameter of men that consumes walnut as compared to those that does not in a human studies with 117 healthy men, aged 21 to 35, participating in a randomized trial (Robbins *et al.*, 2012). In a study, 42 grams of walnuts was added to the diet of adult males, it was found to enhanced sperm motility and concentration. The study showed the important unsaturated fatty acids including alpha-linolenic acid (ALA), omega-3 and omega-6 that are abundant in walnut oil (Robbins *et al.*, 2019).

African yellow wood (*Enantia chlorantha* Oliv.): African yellow wood or *Enatia chlorantha* is a widespread species found in Nigeria's forest. It is a member of the Annonaceae family. The plant extract has been used extensively in traditional medicine, particularly in Nigeria's rural areas, to treat a wide range of human diseases (Akinwale *et al.*, 2022). The effects of oral administration of the stem bark extract of *Enantia chlorantha* at doses of 50 and 100 mg/kg body weight per day for a week on adult albino rats' cause increase in sperm motility, counts, and viability were examined (Salman, 2008).

Bitter kola (*Garcinia kola*): The forest tree *Garcinia kola* Heckel, is native to sub-Saharan Africa with medicinal usefulness. In Nigeria, it is frequently referred to as Bitter Kola (Mavnourová *et al.*, 2019). Chemical analysis revealed that kolaviron is the major component that has help in male reproductive function in male Wistar rat. Administration of Kolaviron an extract from *Garcinia kola* protects rats against ethylene glycol monoethyl ether-induced male reproductive toxicity as evidenced by improvement in spermatozoa number and quality as well as antioxidant status (Adedara and Farombi, 2012). Another extract of *Garcinia kola* is *Garcinia* hydroxybiflavanol 1 (GB1) that increased testosterone, GnRH, FSH, LH, and sperm quality level in the Cadmium chloride treated rat. These results suggest that the Wistar rat testes were protected by the GB1 extract (Abiaezute *et al.*, 2021).

Date Palm (*Phoenix dactylifera* L.): Date palm is a perennial woody plant species that belongs to the Arecaceae family which is edible but with a lot of medicinal uses. It has a significant percentage of sugar and carbohydrates, proteins, fatty acids, salt, vitamins and minerals like potassium and magnesium. It also has high dietary fibre. The vitamins present includes riboflavin, biotin, thiamin, and ascorbic acid, anthocyanins, phenolics, sterols, carotenoids, and flavonoids (Ikefuna, 2002). Date Palm Pollen Extract (DPP) was found to improve the spermogram of Wistar rats that were exposed to electromagnetic fields (EMFs). EMFs negatively affected the sperm count, viability, motility, and testosterone levels in the rats. In another study, male Wistar rats was made infertile by exposure to cypermethrin, following exposure to extract of the Date fruitther was increased percentage motility and a

decrease in total abnormal sperm cells compare to the control. (Ubah, 2021).

Furthermore, another study showed that the Phoenix dactylifera pollen aqueous extract can be used as a sex enhancer, thus act as aphrodisiac, treat pre-ejaculation and impotence, despite these potentials, it has no deleterious effect on the prostate, the seminal vesicle, or the histology of the reproductive tissues (Baharin *et al.*, 2020). In a clinical study, twenty men with normal sperm counts and 60 males with infertility were recruited for the clinical experiment. The participants in the treatment group received daily DPP doses of 400 mg/kg in the form of gelatin capsules for 30 days at the conclusion of the study, and semen samples were taken. Nuclear factor erythroid 2-related factor 2(NRF2), superoxide dismutase (SOD2), glutathione peroxidase 4(GPX4), and catalase (CAT) mRNA expression levels were elevated following DPP therapy. Also, Phoenix dactylifera pollen has antioxidant potential because it increased the expressions of antioxidant gene along with improvements in semen (Abu *et al.*, 2019).

Coconut palm (*Cocos nucifera L.*) Arecaceae): The coconut palm (*Cocos nucifera L.*) Arecaceae) is commonly found in tropics and the water in the nut contains cysteine, an amino acid that is needed for glutathione metabolism which support reproductive processes. Coconut palm (*Cocos nucifera L.*) contains; minerals, carbohydrates, cytokinins, auxins, amino acids, enzymes, and other compounds(DebMandal & Mandal, 2011). The impact of *Cocos nucifera* hydroalcoholic extract on infertility in male rats caused by administration of ceric sulphate was investigated. *C. nucifera* prevented reduction in sexual behavior, testosterone, DHT and poor spermogram and together with. Because of its effect on sexual activity, it can be considered for aphrodisiac uses. *C. nucifera* oil was found to have good ameliorative potential in lead acetate-induced reproductive toxicity in sexually mature male Wistar rats. The polyphenol content and antioxidant activities of the oil are considered to be responsible for the restorative and medical effect of the oil (Olaniyan, 2022).

Baobabs (*Adansonia digitata L.*): Baobabs, or *Adansonia digitata L.*, also known as the African baobab. It is of both medicinal use and food. Almost every part is useful; seed oil. Fruit, leaves, and bark are all significant sources of nutrients and fiber. Aqueous extract of *A. digitata* has antioxidant and anti-inflammatory capacity by its ability to prevent and treat the testicular damage caused on by cotton seed extract treatment. In different experiments, where cadmium chloride, cotton seed extract treatment and dexamethasone and carbon tetrachloride were used to induce testiculopathy in Wistar rats, after the rats were treated with this extract, there was reversal of the pathology. In the study done by Dare *et al* (2021), testiculopathy was induced by single dose 2 mg/kg b.w cadmium chloride intraperitoneally in Wistar rat, some groups were treated with 800 mg/kg *A. digitata* only for 21 day. Positive and reversal of the testicular damage was recorded after the animal were sacrificed (Dare, 2022). The ameliorative effects of the plant manifest by improving the reproductive hormonal parameters, increasing the activity of an antioxidant enzyme, and improvement in the cyto-architecture of the testis (Atuadu, 2021).

CONCLUSION

Male infertility is an important global public health problem and the outcomes of drug treatment for male infertility remain conjectural, with controversial study results. Intrauterine insemination and assisted reproductive therapies such as in vitro fertilization and intracytoplasmic sperm injection are indicated when pharmacological treatments for infertility fail. Because of these circumstances, it's important to look for alternative solutions to this age-old problem. A search through literature and continuous laboratory search for treatment of oligospermia is highly needed.

This review paper describes male infertility and it surrounding complications. It also shows the usefulness of medicinal plants in the management of reproductive anomalies including oligospermias.

REFERENCES

- Abiaezute, C.N., Anya, K. O., Uwagie-Ero, E. A., & Nwaehujor, C. O. (2021). Ameliorative effects of *Garcinia hydroxybiflavanonol 1 (GB1)* isolated from *Garcinia kola* seeds on cadmium chloride (CdCl₂) induced reproductive toxicity in the testis of the male Wistar rats. *Comparative Clinical Pathology*, 30(2), 229–240.
- Abu Elnaga, N. A., Sarhan, M., & Mansour, H. (2019). Teratogenicity of monosodium glutamate on the pregnant rats and their fetuses. *The Egyptian Journal of Hospital Medicine*, 74(8), 1737–1747.
- Acton, Q. A. (2012). *Enzymes and Coenzymes: Advances in Research and Application: 2011 Edition*.
- Adedara, I. A., & Farombi, E. O. (2012). Chemoprotection of ethylene glycol monoethyl ether-induced reproductive toxicity in male rats by kolaviron, isolated biflavonoid from *Garcinia kola* seed. *Human & Experimental Toxicology*, 31(5), 506–517.
- Ahmed, S., Khan, A. A., Yadav, P., Akhtar, J., Akram, U., & Shamim, L. F. (2020). *Gokhru (Tribulus terrestris Linn.): Pharmacological actions and therapeutic applications: A Review. International Journal of Herbal Medicine*, 2020.
- Aiceles, V., & da Fonte Ramos, C. (2016). A link between hypothyroidism, obesity and male reproduction. *Hormone Molecular Biology and Clinical Investigation*, 25(1), 5–13.
- Ainehchi, N., Khaki, A., Farshbaf-Khalili, A., Hammadeh, M., & Ouladsahebmadarek, E. (2019). The effectiveness of herbal mixture supplements with and without clomiphene citrate in comparison to clomiphene citrate on serum antioxidants and glycemic biomarkers in women with polycystic ovary syndrome willing to be pregnant: a randomized clinical tri. *Biomolecules*, 9(6), 215.
- Akang, E., Oremosu, A., Dosumu, O., & Ejiwunmi, A. (2011). *Telfairia Occidentalis*, a Prophylactic Medicine for Alcohol's Damaging Effect on the Testis. *Macedonian Journal of Medical Sciences*, 4(4).
- Akingbade, A. M., Ojewale, A. O., Idhirhi, A., Olasehinde, O. R., Ibitoye, O. B., & okikioluwa Adeyelu, S. (2017). Testiculotoxicity activities of isopropyl alcohol-based air

- freshener on the testis of adult Wistar rats. *Journal of Molecular Pathophysiology*, 6(2), 17–23.
- Akinwale, S. G., Chukwu, O. E., Chioma, O. P., Chukudi, A. J., & Olubunmi, A. G. (2022). *Enantia chlorantha*: A review. *Journal of Pharmacognosy and Phytochemistry*, 11(3), 34–38.
- Alahmadi, B. A. (2020). Effect of Herbal Medicine on Fertility Potential in Experimental Animals-an Update Review. *Materia Socio-Medica*, 32(2), 140.
- Alahmar, A., Dutta, S., Sengupta, P., & others. (2019). Thyroid hormones in male reproduction and infertility. *Asian Pacific Journal of Reproduction*, 8(5), 203.
- Alizadeh, H., Khaki, A., Farzadi, L., Nouri, M., AHMADI, A. Y., SEYEDGHIASI, G., & Shahnazi, V. (2015). The therapeutic effects of a medicinal plant mixture in capsule form on catalase levels in the semen of men with oligospermia.
- Amiri, M., Tehrani, F. R., Nahidi, F., Kabir, A., Azizi, F., & others. (2018). Comparing the effects of combined oral contraceptives containing progestins with low androgenic and antiandrogenic activities on the hypothalamic-pituitary-gonadal axis in patients with polycystic ovary syndrome: systematic review and meta-analysis. *JMIR Research Protocols*, 7(4), e9024.
- Anawalt, B. D., Braunstein, G. D., Gardner, D. G., & Shoback, D. (2017). *Testes*. Greenspan's Basic & Clinical Endocrinology. 10th Ed. New York, NY: McGraw-Hill Education.
- Ansari, M. S., & Almalki, M. H. (2016). Primary hypothyroidism with markedly high prolactin. *Frontiers in Endocrinology*, 7, 35.
- Arab, D., Doustmohammadi, H., & Ardestani Zadeh, A. (2021). Dietary supplements in the management of varicocele-induced infertility: A review of potential mechanisms. *Andrologia*, 53(1), e13879.
- Aykan, D. A., Yaylali, A., Eser, N., Seyithanoglu, M., Yaman, S., & Aykan, A. C. (2020). The effects of sacubitril/valsartan and ramipril on the male fertility in hypertensive rats. *Northern Clinics of Istanbul*, 7(5), 425.
- Ayobami, D., Olaniyan, O., Salihu, M., & Illesanmi, K. (2019). L-ergothioneine supplement protect testicular functions in cisplatin-treated Wistar rats. *J. Pharm. Biol. Sci*, 14, 6–13.
- Ayodeji, A. E., & Aliyu, N. (2018). *Tetracarpidium conophorum* (African walnut) Hutch. & Dalziel: Ethnomedicinal uses and its therapeutic activities. *Journal of Medicinal Plants for Economic Development*, 2(1), 1–10.
- Baharin, A., Hashim, N. E., Sonsudin, F., & Hashim, N. H. (2020). Morphine and *Phoenix dactylifera* (dates) effects on the histological features of male rat reproductive organs. *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences*, 25.
- Benammar, A., Derisoud, E., Vialard, F., Palmer, E., Ayoubi, J. M., Poulain, M., & Chavatte-Palmer, P. (2021). The Mare: A Pertinent Model for Human Assisted Reproductive Technologies? *Animals*, 11(8), 2304.
- Blendon, R. J., & Benson, J. M. (2018). The public and the opioid-abuse epidemic. *New England Journal of Medicine*, 378(5), 407–411.
- Bridges, N., Trofimenko, V., Fields, S., Carrell, D., Aston, K., & Hotaling, J. (2015). Male factor infertility and clomiphene citrate: A meta-analysis—the effect of clomiphene citrate on oligospermia. *Urology Practice*, 2(4), 199–205.
- Cangiano, B., Swee, D. S., Quinton, R., & Bonomi, M. (2021). Genetics of congenital hypogonadotropic hypogonadism: peculiarities and phenotype of an oligogenic disease. *Human Genetics*, 140(1), 77–111.
- Chan, K. (2021). Effects of *Eurycoma longifolia* supplementation: An evaluation of cell growth, exercise performance and wellbeing in adult males. Liverpool John Moores University (United Kingdom).
- Chijoke, O. C., Assumpta, A. C., Lawrence, E., & Sunday, U. (2017). Effect of black walnut (*Tetracarpidium conophorum*) leaf extract on the reproductive organ of male albino rats. *International Journal of Homeopathy and Natural Medicine*, 3(2), 9–14.
- Choy, J. T., & Amory, J. K. (2020). Nonsurgical management of oligozoospermia. *The Journal of Clinical Endocrinology & Metabolism*, 105(12), e4194–e4207.
- Cohen, J., Nassau, D. E., Patel, P., & Ramasamy, R. (2020). Low testosterone in adolescents & young adults. *Frontiers in Endocrinology*, 10, 916.
- Çoyan, K., Ba\csp\inar, N., Bucak, M. N., & Akal\in, P. P. (2011). Effects of cysteine and ergothioneine on post-thawed Merino ram sperm and biochemical parameters. *Cryobiology*, 63(1), 1–6.
- Darbandi, M., Darbandi, S., Agarwal, A., Sengupta, P., Durairajanayagam, D., Henkel, R., & Sadeghi, M. R. (2018). Reactive oxygen species and male reproductive hormones. *Reproductive Biology and Endocrinology*, 16(1), 1–14.
- DebMandal, M., & Mandal, S. (2011). Coconut (*Cocos nucifera* L.: Arecaceae): in health promotion and disease prevention. *Asian Pacific Journal of Tropical Medicine*, 4(3), 241–247.
- Del Giudice, F., Busetto, G. M., De Berardinis, E., Sperduti, I., Ferro, M., Maggi, M., Gross, M. S., Sciarra, A., & Eisenberg, M. L. (2020). A systematic review and meta-analysis of clinical trials implementing aromatase inhibitors to treat male infertility. *Asian Journal of Andrology*, 22(4), 360.
- Dharvind, B. (2019). In vitro & in nivo anti-adipogenic effects of a standardized quassinoid composition from *Eurycoma longifolia*/Dharvind Balan.
- Dimakopoulou, A., Foran, D., Jayasena, C. N., & Minhas, S. (2021). Stimulation of Leydig and Sertoli cellular secretory function by anti-oestrogens: Tamoxifen. *Current Pharmaceutical Design*, 27(23), 2682–2691.
- Divya, B. J., Suman, B., Venkataswamy, M., & ThyagaRaju, K. (2017). The traditional uses and pharmacological activities of *Mucuna pruriens* (L) DC: a comprehensive review. *Indo American Journal of Pharmaceutical Research*, 7(01), 7516–7525.
- Earl, J. A., & Kim, E. D. (2019). Enclomiphene citrate: A treatment that maintains fertility in men with secondary hypogonadism. *Expert Review of Endocrinology & Metabolism*, 14(3), 157–165.
- El Meliegy, A., Motawi, A., & Abd El Salam, M. A. (2018). Systematic review of hormone replacement therapy in the infertile man. *Arab Journal of Urology*, 16(1), 140–147.
- Engels, M., Gehrmann, K., Falhammar, H., Webb, E. A., Nordenström, A., Sweep, F. C., Span, P. N., van

- Herwaarden, A. E., Rohayem, J., Richter-Unruh, A., & others. (2018). Gonadal function in adult male patients with congenital adrenal hyperplasia. *European Journal of Endocrinology*, 178(3), 285–294.
- Eskandari, D., Khodabandehloo, N., Gholami, A., Samadanifard, H., & Hejrati, A. (2020). Investigation of the association between metabolic syndrome and breast cancer patients. *European Journal of Translational Myology*, 30(1).
- Farmakiotis, D., Farmakis, C., Rousso, D., Kourtis, A., Katsikis, I., & Panidis, D. (2007). The beneficial effects of toremifene administration on the hypothalamic-pituitary-testicular axis and sperm parameters in men with idiopathic oligozoospermia. *Fertility and Sterility*, 88(4), 847–853.
- Fausser, B., Bogers, J. W., Hop, W. C. J., & De Jong, F. H. (1990). Bioactive and immunoreactive FSH in serum of normal and oligospermic men. *Clinical Endocrinology*, 32(4), 433–442.
- Fernandez, C. J., Chacko, E. C., & Pappachan, J. M. (2019). Male obesity-related secondary hypogonadism--pathophysiology, clinical implications and management. *European Endocrinology*, 15(2), 83.
- Fink, J., Schoenfeld, B. J., Hackney, A. C., Maekawa, T., & Horie, S. (2021). Human chorionic gonadotropin treatment: a viable option for management of secondary hypogonadism and male infertility. *Expert Review of Endocrinology & Metabolism*, 16(1), 1–8.
- Gonçalves, C., Cunha, M., Rocha, E., Fernandes, S., Silva, J., Ferraz, L., Oliveira, C., Barros, A., & Sousa, M. (2017). Y-chromosome microdeletions in nonobstructive azoospermia and severe oligozoospermia. *Asian Journal of Andrology*, 19(3), 338.
- Hahner, S., Ross, R. J., Arlt, W., Bancos, I., Burger-Stritt, S., Torpy, D. J., Husebye, E. S., & Quinkler, M. (2021). Adrenal insufficiency. *Nature Reviews Disease Primers*, 7(1), 1–24.
- Hammes, S. R., Levin, E. R., & others. (2019). Impact of estrogens in males and androgens in females. *The Journal of Clinical Investigation*, 129(5), 1818–1826.
- Hart, R. J., Doherty, D. A., Mori, T. A., Adams, L. A., Huang, R.-C., Minaee, N., Handelsman, D. J., McLachlan, R., Norman, R. J., Dickinson, J. E., & others. (2019). Features of the metabolic syndrome in late adolescence are associated with impaired testicular function at 20 years of age. *Human Reproduction*, 34(3), 389–402.
- Hussain, S. A., Hameed, A., Nasir, F., Wu, Y., Suleria, H. A. R., & Song, Y. (2018). Evaluation of the spermatogenic activity of polyherbal formulation in oligospermic males. *BioMed Research International*, 2018.
- Ikefuna, A. N., & Emodi, I. J. (2002). An assessment of factors influencing hospital discharges against medical advice of paediatric patients in enugu: a review of 67 cases. *Nigerian Journal of Paediatrics*, 29(1), 1–4.
- Jain, G. C., & Jangir, R. N. (2014). Modulation of diabetes-mellitus-induced male reproductive dysfunctions in experimental animal models with medicinal plants. *Pharmacognosy Reviews*, 8(16), 113.
- Javorsky, B. R., Raff, H., Carroll, T. B., Algeciras-Schimmich, A., Singh, R. J., Colón-Franco, J. M., & Findling, J. W. (2021). New cutoffs for the biochemical diagnosis of adrenal insufficiency after ACTH stimulation using specific cortisol assays. *Journal of the Endocrine Society*, 5(4), bvab022.
- Kadioglu, T. C. (2009). Oral tamoxifen citrate treatment is more effective in normogonadotropic patients who have follicle-stimulating hormone levels within the lower half of normal. *International Urology and Nephrology*, 41(4), 773–776.
- Kaminetsky, J., Werner, M., Fontenot, G., & Wiehle, R. D. (2013). Oral enclomiphene citrate stimulates the endogenous production of testosterone and sperm counts in men with low testosterone: comparison with testosterone gel. *The Journal of Sexual Medicine*, 10(6), 1628–1635.
- Kasman, A. M., Zhang, C. A., Li, S., Stevenson, D. K., Shaw, G. M., & Eisenberg, M. L. (2020). Association of preconception paternal health on perinatal outcomes: analysis of US claims data. *Fertility and Sterility*, 113(5), 947–954.
- Klami, R., Mankonen, H., & Perheentupa, A. (2018). Successful microdissection testicular sperm extraction for men with non-obstructive azoospermia. *Reproductive Biology*, 18(2), 137–142.
- La Vignera, S., Vita, R., Condorelli, R. A., Mongio\`i, L. M., Presti, S., Benvenega, S., & Calogero, A. E. (2017). Impact of thyroid disease on testicular function. *Endocrine*, 58(3), 397–407.
- Lazzaroni, M.-G., Crisafulli, F., Moschetti, L., Semeraro, P., Cunha, A.-R., Neto, A., Lojacono, A., Ramazzotto, F., Zanardini, C., Zatti, S., & others. (2022). Reproductive Issues and Pregnancy Implications in Systemic Sclerosis. *Clinical Reviews in Allergy & Immunology*, 1–22.
- Lopez, E. O., Parmar, M., Pendela, V. S., & Terrell, J. M. (2022). Lisinopril. In StatPearls [Internet]. StatPearls Publishing.
- Mal\vnurova, A., Leuner, O., Tchoundjeu, Z., Van Damme, P., Verner, V., P\vribyl, O., & Lojka, B. (2019). Medicinal potential, utilization and domestication status of bitter kola (*Garcinia kola* Heckel) in West and Central Africa. *Forests*, 10(2), 124.
- Malviya, N., Malviya, S., Jain, S., & Vyas, S. (2016). A review of the potential of medicinal plants in the management and treatment of male sexual dysfunction. *Andrologia*, 48(8), 880–893.
- Mancini, A., & Balercia, G. (2011). Coenzyme Q10 in male infertility: physiopathology and therapy. *Biofactors*, 37(5), 374–380.
- Mandal, A., Chattopadhyay, S., Sasmal, C., Maiti, T. K., & Bhattacharyya, S. (2020). Effects of clomiphene citrate on seminal parameters in idiopathic oligospermia: a single blinded prospective randomized controlled trial. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, 9(1), 94–99.
- Mandlik, D. S., & Namdeo, A. G. (2021). Pharmacological evaluation of Ashwagandha highlighting its healthcare claims, safety, and toxicity aspects. *Journal of Dietary Supplements*, 18(2), 183–226.
- Martins, R. V. L., Silva, A., Duarte, A. P., Socorro, S., Correia, S., & Maia, C. J. (2021). Natural Products as Protective Agents for Male Fertility. *BioChem*, 1(3), 122–147.
- Mbah, A. U., Ndukwu, G. O., Ghasi, S. I., Shu, E. N., Ozoemena, F. N., Mbah, J. O., Onodugo, O. D., Ejim, E. C., Eze, M. I., Nkwo, P. O., & others. (2012). Low-dose lisinopril in normotensive men with idiopathic oligospermia

- and infertility: a 5-year randomized, controlled, crossover pilot study. *CLInICAL PhArmACOLoGY \& TherApeUTICs*, 91(4), 582–589.
- Meenakshi, S. C., Beldal, B. S., & Londonkar, R. L. (2019). Review on ethnobotany phytoconstituents and phytopharmacology of *Bombax ceiba* Linn. *Int J Pharm Biol Sci*, 9, 1061–1066.
- Mehta, A., & Sigman, M. (2015). Management of the dry ejaculate: a systematic review of aspermia and retrograde ejaculation. *Fertility and Sterility*, 104(5), 1074–1081.
- Mieusset, R., Bieth, E., Daudin, M., Isus, F., Delaunay, B., Bujan, L., Monteil, L., Fauquet, I., Huyghe, E., & Hamdi, S. M. (2020). Male partners of infertile couples with congenital unilateral absence of the vas deferens are mainly non-azoospermic. *Andrology*, 8(3), 645–653.
- Modgil, V., Rai, S., Ralph, D. J., & Muneer, A. (2016). An update on the diagnosis and management of ejaculatory duct obstruction. *Nature Reviews Urology*, 13(1), 13–20.
- Nezhad, N. C., Vahabzadeh, Z., Allahveisie, A., Rahmani, K., Raofi, A., Rezaie, M. J., Rezaei, M., & Partovyan, M. (2021). The effect of L-carnitine and coenzyme Q10 on the sperm motility, DNA fragmentation, chromatin structure and oxygen free radicals during, before and after freezing in Oligospermia men. *Urology Journal*, 18(03), 330–336.
- Noh, S., Go, A., Kim, D. Bin, Park, M., Jeon, H. W., & Kim, B. (2020). Role of antioxidant natural products in management of infertility: a review of their medicinal potential. *Antioxidants*, 9(10), 957.
- Nsagha, D. S., Ayima, C. W., Nana-Njamen, T., & Assob, J. C. N. (2020). The role of traditional, complementary/alternative medicine in primary healthcare, adjunct to universal health coverage in Cameroon: a review of the literature. *American Journal of Epidemiology*, 8(1), 37–47.
- Okoro, D. C. (2020). African Women and the Shame and Pain of Infertility: An Ethico-cultural Study of Christian Response to Childlessness among the Igbo People of West Africa. *Wipf and Stock Publishers*.
- Olaniyan, O. T., Dare, A., Okotie, G. E., Adetunji, C. O., Ibitoye, B. O., Bamidele, O. J., & Eweoya, O. O. (2020). Testis and blood-testis barrier in Covid-19 infestation: role of angiotensin-converting enzyme 2 in male infertility. *Journal of Basic and Clinical Physiology and Pharmacology*, 31(6).
- Olaolu, T., Ogu, T., Rotimi, D., Nwonuma, C., Awakan, O., Olaolu, A., & Akpor, O. (2022). Amelioration of cadmium chloride testicular toxicity by *Plukenetia conophora* aqueous leaves extract in Wistar rats. *Thai Journal of Pharmaceutical Sciences (TJPS)*, 46(3).
- Organization, W. H., & others. (2021). WHO laboratory manual for the examination and processing of human semen. *World Health Organization*.
- Parsa, A. A., & New, M. I. (2017). Steroid 21-hydroxylase deficiency in congenital adrenal hyperplasia. *The Journal of Steroid Biochemistry and Molecular Biology*, 165, 2–11.
- Pilny, A. A. (2014). Endocrinology, An Issue of Veterinary Clinics: Exotic Animal Practice.
- Puia, D., & Pricop, C. (2022). Effectiveness of Clomiphene Citrate for Improving Sperm Concentration: A Literature Review and Meta-Analysis. *Cureus*, 14(5).
- Punab, M., Poolamets, O., Paju, P., Vihljajev, V., Pomm, K., Ladva, R., Korrovits, P., & Laan, M. (2017). Causes of male infertility: a 9-year prospective monocentre study on 1737 patients with reduced total sperm counts. *Human Reproduction*, 32(1), 18–31.
- Punjani, N., Kang, C., & Schlegel, P. N. (2020). Clinical implications of Y chromosome microdeletions among infertile men. *Best Practice \& Research Clinical Endocrinology \& Metabolism*, 34(6), 101471.
- Rastrelli, G., Lotti, F., Reisman, Y., Sforza, A., Maggi, M., & Corona, G. (2019). Metabolically healthy and unhealthy obesity in erectile dysfunction and male infertility. *Expert Review of Endocrinology \& Metabolism*, 14(5), 321–334.
- Ribas-Maynou, J., & Yeste, M. (2020). Oxidative stress in male infertility: causes, effects in assisted reproductive techniques, and protective support of antioxidants. *Biology*, 9(4), 77.
- Ring, J. D., Lwin, A. A., & Köhler, T. S. (2016). Current medical management of endocrine-related male infertility. *Asian Journal of Andrology*, 18(3), 357.
- Robbins, W. A., Xun, L., FitzGerald, L. Z., Esguerra, S., Henning, S. M., & Carpenter, C. L. (2012). Walnuts improve semen quality in men consuming a Western-style diet: randomized control dietary intervention trial. *Biology of Reproduction*, 87(4), 101.
- Robbins, W., Kim, H., Houman, J., & Lee, G.-W. (2019). Randomized clinical trial: effect of walnuts on semen parameters and male fertility (P18-042-19). *Current Developments in Nutrition*, 3(Supplement_1), nzz039--P18.
- Rosenthal, L., Hernandez, P., & Vaamonde, D. (2022). Traditional Chinese medicine, Ayurveda, and fertility. *Fertility, Pregnancy, and Wellness*, 209–247.
- Sadat-Ebrahimi, S.-R., Parnianfard, N., Vahed, N., Babaei, H., Ghojzadeh, M., Tang, S., & Azarpazhooh, A. (2018). An evidence-based systematic review of the off-label uses of lisinopril. *British Journal of Clinical Pharmacology*, 84(11), 2502–2521.
- Salman, T. M., & Adesokan, A. A. (2008). Sperm quality of male rats treated with aqueous extract of *Enantia chlorantha* stem bark. *African Journal of Biotechnology*, 7(7).
- Salzano, A., D’Assante, R., Heaney, L. M., Monaco, F., Rengo, G., Valente, P., Pasquali, D., Bossone, E., Gianfrilli, D., Lenzi, A., & others. (2018). Klinefelter syndrome, insulin resistance, metabolic syndrome, and diabetes: review of literature and clinical perspectives. *Endocrine*, 61(2), 194–203.
- Samperi, I., Lithgow, K., & Karavitaki, N. (2019). *Hyperprolactinaemia*. *Journal of Clinical Medicine*, 8(12), 2203.
- Shankara-Narayana, N., Di Pierro, I., Fennell, C., Ly, L. P., Bacha, F., Vrga, L., Savkovic, S., Turner, L., Jayadev, V., Conway, A. J., & others. (2019). Sperm cryopreservation prior to gonadotoxic treatment: experience of a single academic centre over 4 decades. *Human Reproduction*, 34(5), 795–803.
- Sharma, A. P., Sharma, G., & Kumar, R. (2021). Systematic review and meta-analysis on effect of Carnitine, Coenzyme Q10 and Selenium on pregnancy and semen parameters in couples with idiopathic male infertility. *Urology*.
- Singh, K., Singh, A., & Sarada, A. K. (2013). Assessment of mesterolone therapy in oligospermic males. *International Journal of Pharmaceutical Science Invention*, 2(3), 17–21.

- Tafari, S., Cocchia, N., Vasseti, A., Carotenuto, D., Esposito, L., Maruccio, L., Avallone, L., & Ciani, F. (2021). *Lepidium meyenii* (Maca) in male reproduction. *Natural Product Research*, 35(22), 4550–4559.
- Taghizadeh, L., Eidi, A., Mortazavi, P., & Rohani, A. H. (2017). Effect of selenium on testicular damage induced by varicocele in adult male Wistar rats. *Journal of Trace Elements in Medicine and Biology*, 44, 177–185.
- Tambi, M. I. B. M., & Imran, M. K. (2010). *Eurycoma longifolia* Jack in managing idiopathic male infertility. *Asian Journal of Andrology*, 12(3), 376.
- Terai, K., Horie, S., Fukuhara, S., Miyagawa, Y., Kobayashi, K., & Tsujimura, A. (2020). Combination therapy with antioxidants improves total motile sperm counts: A Preliminary Study. *Reproductive Medicine and Biology*, 19(1), 89–94.
- Tharakan, T., Salonia, A., Corona, G., Dhillon, W., Minhas, S., & Jayasena, C. (2020). The role of hormone stimulation in men with nonobstructive azoospermia undergoing surgical sperm retrieval. *The Journal of Clinical Endocrinology & Metabolism*, 105(12), e4896–e4906.
- Tirabassi, G., Vignini, A., Tiano, L., Buldreghini, E., Brugè, F., Silvestri, S., Orlando, P., D’Aniello, A., Mazzanti, L., Lenzi, A., & others. (2015). Protective effects of coenzyme Q10 and aspartic acid on oxidative stress and DNA damage in subjects affected by idiopathic asthenozoospermia. *Endocrine*, 49(2), 549–552.
- Tournaye, H., Krausz, C., & Oates, R. D. (2017). Novel concepts in the aetiology of male reproductive impairment. *The Lancet Diabetes & Endocrinology*, 5(7), 544–553.
- Tsampoukas, G., Gkeka, K., Dellis, A., Brown, D., Katsouri, A., Alneshawy, A., Moussa, M., Papatsoris, A., & Buchholz, N. (2021). Vitamins as primary or adjunctive treatment in infertile men with varicocele: A systematic review. *Arab Journal of Urology*, 19(3), 264–273.
- Vander Borght, M., & Wyns, C. (2018). Fertility and infertility: Definition and epidemiology. *Clinical Biochemistry*, 62, 2–10.
- Varma, T. R., & Patel, R. H. (1988). The effect of mesterolone on sperm count, on serum follicle stimulating hormone, luteinizing hormone, plasma testosterone and outcome in idiopathic oligospermic men. *International Journal of Gynecology & Obstetrics*, 26(1), 121–128.
- Wheeler, K. M., Sharma, D., Kavoussi, P. K., Smith, R. P., & Costabile, R. (2019). Clomiphene citrate for the treatment of hypogonadism. *Sexual Medicine Reviews*, 7(2), 272–276.
- Wiehle, R. D., Fontenot, G. K., Wike, J., Hsu, K., Nydell, J., Lipshultz, L., Group, Z.-203 C. S., & others. (2014). Enclomiphene citrate stimulates testosterone production while preventing oligospermia: a randomized phase II clinical trial comparing topical testosterone. *Fertility and Sterility*, 102(3), 720–727.
- Xu, X., Sun, M., Ye, J., Luo, D., Su, X., Zheng, D., Feng, L., Gao, L., Yu, C., & Guan, Q. (2017). The effect of aromatase on the reproductive function of obese males. *Hormone and Metabolic Research*, 49(08), 572–579.
- Yilmaz, S., Yilmaz Sezer, N., Gönenç, İlknur Münevver, İlhan, S. E., & Yilmaz, E. (2018). Safety of clomiphene citrate: a literature review. *Cytotechnology*, 70(2), 489–495.
- Yu, J., Chen, Z., Ni, Y., & Li, Z. (2012). CFTR mutations in men with congenital bilateral absence of the vas deferens (CBAVD): a systemic review and meta-analysis. *Human Reproduction*, 27(1), 25–35.