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HARNESSING PHYTOTHERAPY: EXPLORING ALTERNATIVE TREATMENTS FOR MALE INFERTILITY

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ВИКОРИСТАННЯ ФІТОТЕРАПІЇ: ВИВЧЕННЯ АЛЬТЕРНАТИВНИХ МЕТОДІВ ЛІКУВАННЯ ЧОЛОВІЧОГО БЕЗПЛІДДЯ

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ABSTRACT

Purpose: The multifaceted nature of male infertility requires innovative approaches, leading researchers to explore the potential of phytotherapy to improve reproductive health. Phytotherapy offers a promising prospect for individuals seeking alternative treatments for male infertility, harnessing the natural therapeutic properties of plant-based compounds. The aim of this work is to investigate the efficacy and mechanisms of action of phytotherapy as a promising alternative treatment for male infertility. Through a comprehensive review of existing literature and clinical trials, this research aims to elucidate the potential benefits of phytotherapeutic interventions in improving sperm quality, enhancing reproductive parameters and addressing the underlying causes of male infertility.

Methodology. We conducted a comprehensive literature search using electronic databases including PubMed, Scopus, Web of Science and Google Scholar. The search was conducted from 1970 to 2024, with no language restrictions. The following keywords and combinations of keywords were used: "phytotherapy", "male infertility", "herbal medicine", "plant extracts", "natural remedies" and "herbal supplements". In addition, relevant articles were identified through manual searches of the reference lists of the retrieved trials and review articles. Articles were included if they met the following criteria: (1) original research articles, systematic reviews, meta-analyses and clinical trials investigating the efficacy of phytotherapy in the treatment of male infertility; (2) studies reporting outcomes related to sperm quality, reproductive hormones, semen parameters or fertility outcomes; (3) human studies involving adult men diagnosed with infertility or subfertility; (4) studies published in peer-reviewed journals.

Scientific novelty. While conventional treatments for male infertility often focus on hormonal therapies, surgery or assisted reproductive techniques, this manuscript highlights the potential of phytotherapy as an alternative approach. By exploring natural remedies derived from medicinal plants, this manuscript offers new insights into complementary strategies for the treatment of male infertility. The emphasis on alternative treatments reflects a growing interest in holistic and integrative approaches to reproductive medicine. In addition to discussing the broader concept of phytotherapy, this manuscript examines the efficacy of specific phytochemicals in the treatment of male infertility. By focusing on individual compounds and their pharmacological effects, this manuscript advances our understanding of the bioactive constituents responsible for the therapeutic effects of medicinal plants. This targeted approach allows for a more nuanced evaluation of phytotherapeutic interventions and facilitates the identification of potential drug candidates.

Conclusions. The use of various medicinal plants with benefits for male reproductive health was discussed, including *Tribulus terrestris*, *Apium graveolens*, *Withania somnifera*, *Cornus mas*, *Fumaria parviflora*, *Phoenix dactylifera* and many others, was discussed. The mechanisms by which these herbal remedies may exert their effects on sperm quality, reproductive hormones and overall fertility were also demonstrated. The role of plants as adjunctive therapies to address underlying conditions associated with male infertility, such as oxidative stress, inflammation and hormonal imbalances, was discussed. Although promising, clinical evidence for the efficacy of herbal treatments for male infertility remains limited, highlighting the need for further well-designed clinical trials and studies. Nevertheless, the integration of medicinal plants into comprehensive fertility care protocols offers a promising avenue for improving male reproductive health outcomes and warrants further exploration.

Key words: herbal medicine, male infertility, medicinal plants, phytotherapy, reproductive hormones, sperm quality

АНОТАЦІЯ

Мета: Багатостороння природа чоловічого безпліддя вимагає інноваційних підходів, що спонукає дослідників до вивчення потенціалу фітотерапії для покращення репродуктивного здоров'я. Фітотерапія пропонує багатообіцяючу перспективу для людей, які шукають альтернативні методи лікування чоловічого безпліддя, використовуючи природні терапевтичні властивості рослинних сполук. Метою цієї статті є представлення досліджень ефективності та механізмів дії фітотерапії як перспективного альтернативного лікування чоловічого безпліддя. Завдяки всебічному огляду існуючої літератури та клінічних випробувань це дослідження має на меті з'ясувати потенційні переваги фітотерапевтичних втручань у покращенні якості сперми, репродуктивних параметрів та усуненні основних причин чоловічого безпліддя.

Методологія. Ми провели комплексний пошук літератури за допомогою електронних баз даних, включаючи PubMed, Scopus, Web of Science і Google Scholar. Пошук вівся з 1970 по 2024 рік, без мовних обмежень. Використовувалися наступні ключові слова та їх поєднання: «фітотерапія», «чоловіче безпліддя», «рослинні екстракти», «природні засоби» та «трав'яні добавки». Крім того, відповідні статті були визначені шляхом пошуку в списках посилань на отримані дослідження та оглядові статті. Статті включалися в огляд, якщо вони відповідали таким критеріям: (1) оригінальні дослідницькі статті, систематичні огляди, мета-аналізи та клінічні випробування, що досліджують ефективність фітотерапії в лікуванні чоловічого безпліддя; (2) дослідження, що повідомляють про результати, пов'язані з якістю сперми, репродуктивними гормонами, параметрами сперми або результатами фертильності; (3) дослідження на людях за участю дорослих чоловіків з діагнозом безпліддя або зниження фертильності; (4) дослідження, опубліковані в рецензованих журналах.

Наукова новизна. У той час як звичайні методи лікування чоловічого безпліддя часто зосереджені на гормональній терапії, хірургії або допоміжних репродуктивних методах, ця оглядова стаття підкреслює потенціал фітотерапії як альтернативного підходу. Досліджуючи природні компоненти, отримані з лікарських рослин, ця стаття пропонує нове уявлення про додаткові стратегії лікування чоловічого безпліддя. Акцент на альтернативних методах лікування відображає зростаючий інтерес до цілісних та інтегративних підходів до репродуктивної медицини. Окрім обговорення ширшої концепції фітотерапії, у цій статті розглядається ефективність конкретних видів рослин у лікуванні чоловічого безпліддя. Зосереджуючись на окремих сполуках та їхніх фармакологічних ефектах, ця стаття покращує наше розуміння біоактивних компонентів, відповідальних за терапевтичний ефект лікарських рослин. Такий цілеспрямований підхід дозволяє проводити більш детальну оцінку фітотерапевтичних втручань і полегшує ідентифікацію потенційних препаратів-кандидатів.

Висновки. У цій статті обговорено використання різних лікарських рослин, які проявляють потенціал в лікуванні чоловічого безпліддя, в тому числі *Tribulus terrestris*, *Apium graveolens*, *Withania somnifera*, *Cornus mas*, *Fumaria parviflora*, *Phoenix dactylifera* та багато інших. Було також продемонстровано механізми, за допомогою яких ці рослини можуть впливати на якість сперми, репродуктивні гормони та загальну фертильність. Було обговорено роль рослин як допоміжної терапії для лікування основних захворювань, пов'язаних з чоловічим безпліддям, таких як окиснювальний стрес, запалення та гормональний дисбаланс. Незважаючи на багатообіцяючі, клінічні докази ефективності лікування травами чоловічого безпліддя, підкреслюється необхідність подальших добре спланованих клінічних випробувань і досліджень. Тим не менш, інтеграція лікарських рослин у комплексні протоколи моніторингу за фертильністю пропонує багатообіцяючий підхід для покращення результатів чоловічого репродуктивного здоров'я та вимагає подальших досліджень.

Ключові слова: лікарські рослини, репродуктивні гормони, фітотерапія, чоловіче безпліддя, якість сперми

Introduction

Male infertility is becoming an increasingly serious medical problem, although the mechanism of its onset remains poorly understood. Male reproductive dysfunction affects approximately half of infertile couples worldwide (Assidi, 2022). Male infertility is a multifactorial syndrome involving a wide range of disorders, a symptom of many different pathological conditions affecting both the reproductive and other systems of the body: endocrine, nervous, circulatory and immune. Many factors, including the environment, genetics, age and comorbidities, contribute to impaired sperm function (Kamiński et al., 2020; Baszyński et al., 2022; Szymanski et al., 2024). Infertility is a medical condition characterised by the inability of a sexually active couple to conceive after one year or more of regular unprotected intercourse (or six months for women over 35) (Thonneau et al., 1991). In the last decade, the role of oxidative stress in sperm quality has received increased attention and is estimated to be a problem in 25-87 % of male infertility cases (Smits et al., 2020). In this article we will look at male infertility as one of the growing problems of the current generation.

Unfavourable demographic indicators, with a stable negative rate of natural population growth in recent decades, have forced specialists in various fields (geneticists, morphologists, immunologists, endocrinologists, gynae-

cologists and urologists) to turn to the analysis of factors affecting fertility, among which infertility occupies an important place. Infertility affects an estimated 15 % of couples worldwide, or 48.5 million couples. Men are found to be solely responsible for 20-30 % of infertility cases and contribute to 50 % of cases overall. However, this figure does not accurately represent all regions of the world (Agarwal et al., 2015). According to statistics, the frequency of infertile marriages ranges from 8 to 29 % in many countries around the world. In Europe, about 10% of married couples suffer from infertility, in the USA 15 % and in Canada 17 % (Sallmén et al., 2006).

Male infertility is a growing concern within the medical community and represents a significant challenge to reproductive health. The prevalence of this condition is increasing, signalling an urgent need for comprehensive research and proactive intervention strategies (Assidi, 2022). Addressing male infertility requires a multifaceted approach that includes both medical treatments and lifestyle changes. As we face this escalating medical problem, collaboration between healthcare professionals, researchers and those affected by infertility is essential to effectively address this pressing public health issue (Kamiński et al., 2020; Baszyński et al., 2022; Szymanski et al., 2024).

The growing body of evidence supporting the efficacy of phytotherapy in improving sperm quality and reproductive parameters highlights its potential as a valuable alternative treatment for male infertility. Given the limitations and side effects associated with conventional treatments, the study of phytotherapy as an alternative approach to male infertility is gaining traction. This paper aims to investigate the efficacy and mechanisms of action of phytotherapy as a promising alternative treatment for male infertility. Through a comprehensive review of existing literature and clinical trials, this research aims to elucidate the potential benefits of phytotherapeutic interventions in improving sperm quality, enhancing reproductive parameters and addressing the underlying causes of male infertility. In addition, this study aims to identify key phytochemicals and botanical extracts with promising therapeutic properties, paving the way for the development of nature-based therapies to complement existing treatments for male infertility.

Materials and methods

We conducted a comprehensive literature search using electronic databases including PubMed, Scopus, Web of Science and Google Scholar. The search was conducted from 1970 to 2024, with no language restrictions. The following keywords and combinations of keywords were used: “phytotherapy”, “male infertility”, “herbal medicine”, “plant extracts”, “natural remedies” and “herbal supplements”. In addition, relevant articles were identified through manual searches of the reference lists of the retrieved trials and review articles.

Articles were included if they met the following criteria: (1) original research articles, systematic reviews, meta-analyses and clinical trials investigating the efficacy of phytotherapy in the treatment of male infertility; (2) studies reporting outcomes related to sperm quality, reproductive hormones, semen parameters or fertility outcomes; (3) human studies involving adult men diagnosed with infertility or subfertility; (4) studies published in peer-reviewed journals.

Analysis of modern research

Causes of infertility and traditional medical approaches to their elimination

The overall incidence of male factor infertility is estimated to be between 2.5 % and 12 %. In North America, the incidence of male factor infertility is 4.5-6 %, in Australia it is 9 % and in Eastern Europe it can be as high as 8-12 % (Agarwal et al., 2015). In the French population, the prevalence of male factor infertility was 20 %. In the French population, 20 % of all infertility cases were exclusively due to male factors (Agarwal et al., 2015), in Western Siberia 6.4 % (Philippov et al., 1998) and in Nigeria 42.4 % (Ikechebelu et al., 2003). The prevalence of infertility varies, with male infertility being less epidemiologically documented in developing countries.

Biologically, male infertility is related to disorders in the male reproductive system that prevent the successful conception of a child. Here are some of the biological aspects of male infertility (Fig. 1):

✔ Sperm quantity and quality: Too few sperm or poor sperm quality (for example, the inability of sperm to move properly or abnormalities in their structure) can cause infertility;

✔ Abnormalities of the reproductive system: Structural abnormalities in the organs of the reproductive system, such as birth defects, inflammation or injury, can interfere with the normal process of conception;

✔ Hormonal disorders: Disorders in the levels of hormones such as gonadotropins, testosterone and others can affect spermatogenesis and the function of the reproductive organs;

✔ Ejaculation problems: Absent or disturbed ejaculation can result in sperm not being released into the female reproductive system;

✔ Genetic factors: Some cases of male infertility may be due to genetic abnormalities that affect sperm production or function.

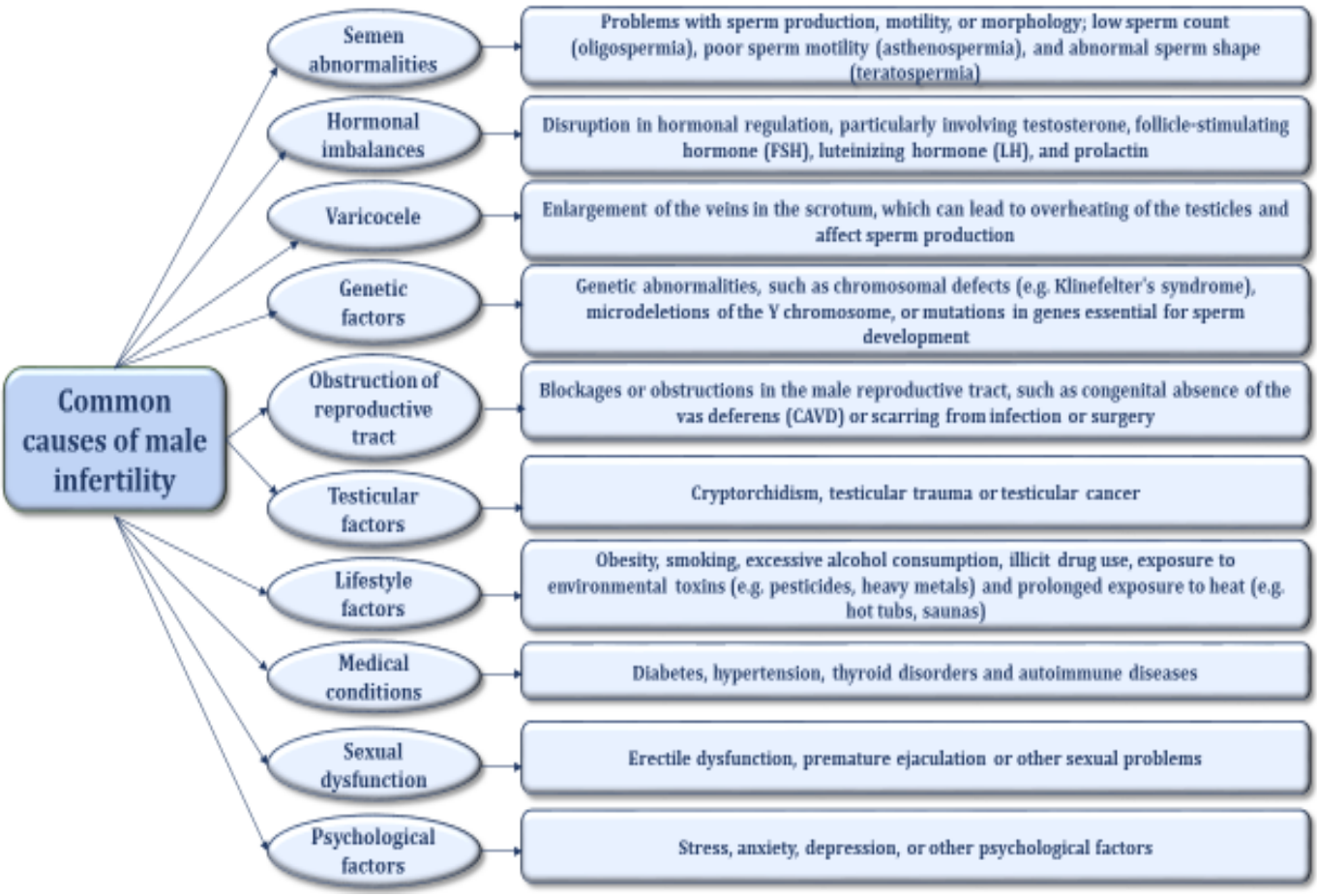

Fig. 1. An overview of the most common causes of male infertility

According to WHO recommendations (2000), 16 main nosologies have been identified, each including up to several dozen specific pathogenetic factors; 4 of the 16 diagnoses are descriptive, without indicating the true cause: idiopathic oligo-, astheno-, terato- and azoospermia. Most of the "idiopathic" forms are genetically determined and associated with mutations and polymerphisms of many genes: sperm development is regulated by more than 2000 genes, only 230 of which are located on the Y chromosome (WHO, 2000; Nuti and Krausz, 2008).

The causes of male infertility fall into three main categories: pre-testicular, testicular and post-testicular. Pre-testicular causes of infertility include extragonadal endocrine disorders such as hypothalamic, pituitary or adrenal disorders that affect spermatogenesis (Wong et al., 1978). Pretesticular causes include hypogonadotropic hypogonadism, erectile dysfunction or coital abnormalities such as retrograde ejaculation, anejaculation, genetic factors and chromosomal abnormalities (Barak and Baker, 2016).

Hypogonadotropic hypogonadism (HH), a less common aetiology compared to other

causes of male infertility, is caused by insufficient secretion of gonadotropin-releasing hormone (GnRH) and/or folliculotropic hormone (FSH) and luteinising hormone (LH) (Oates, 2012). These deficiencies result in impaired androgen secretion and spermato-genesis. HH can be caused by congenital GnRH deficiency, haemochromatosis, genetic disorders, pituitary and hypothalamic tumours, hormonal disorders or medication. In addition, systemic conditions such as chronic diseases, nutritional deficiencies and obesity have been reported as causes of HH (Swee and Quinton, 2019).

Testicular disorders include tumours, orchiectomy, primitive testicular dysfunction, cryptorchidism and atrophic testes. Varicocele is associated with male infertility, most likely due to impaired testicular thermoregulation as a result of disruption of the thermoregulatory mechanism of the pampiniform venous plexus (Stillman, 1982). Epididymal dysfunction may be caused by in utero fetal exposure to estrogens, various drugs and chemical toxins, epididymal cysts, spermatoceles with or without surgery, epididymitis and may also be idiopathic (Hikim et al, 2000). Acquired testicular failure may result from trauma, torsion of the testis, orchitis, exogenous factors (e.g. drugs, systemic diseases, varicocele) or surgery that damages the vascular structure of the testis. Varicoceles are present in about 15 % of men in the general population and about 4 0% of men with male infertility (Oates, 2012). Post-testicular failure, often called obstructive azoospermia, is caused by either ejaculatory dysfunction or obstruction of sperm transport. This form of male infertility is less common than non-obstructive azoospermia, but occurs in around 40 % of men with azoospermia. The obstruction can occur in the epididymis, vas deferens or vas deferens and can be either acquired or congenital (Oates, 2012).

It's important to note that male infertility is often multifactorial, with several factors contributing to reduced fertility. A thorough evaluation by a healthcare provider specializing in male reproductive health, such as a urologist or reproductive endocrinologist, is essential to identify the underlying causes of infertility and develop an appropriate treatment plan (Fig. 2).

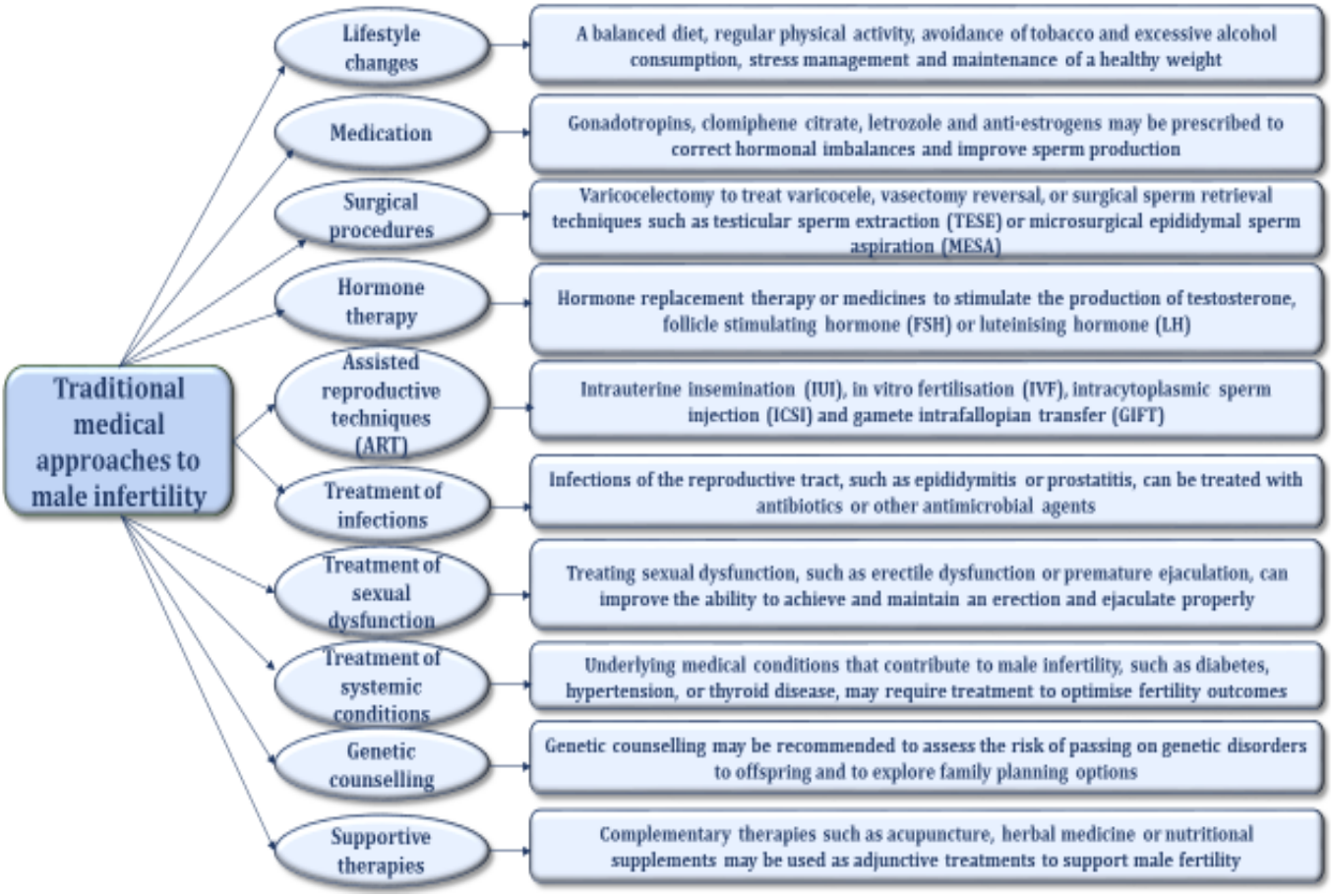

Fig. 2. Traditional medical approaches to male infertility

Prior to surgical sperm retrieval, men with azoospermia are usually prescribed replacement therapy with gonadotropins and antiestrogens, such as selective estrogen receptor modulators (SERMs) and aromatase inhibitors (Corona and Giovanni, 2015). In infertile men with hypogonadotropic hypogonadism (HH) due to lack of hypothalamic secretion (e.g. Kallmann syndrome), gonadotropin-releasing hormone (GnRH) administration replaces the GnRH deficiency. This is done by stimulating the release of FSH and LH from the anterior pituitary. Four months after the start of therapy, GnRH stimulates spermatogenesis very well. In about 85 % of patients, pulsatile GnRH therapy induces spermatogenesis (Blumenfeld et al., 1988). Gonadotropins are used to treat male infertility in men with pituitary insufficiency such as pituitary adenoma and systemic diseases such as haemochromatosis and sarcoidosis. Advances in laboratory technology have made human chorionic gonadotropin (rec-hCG), FSH (rec-hFSH) and LH (rec-hLH) more effective. Most studies show that gonadotropins induce spermatogenesis in about 80 % of men (Miyagawa et al., 2005).

Dopamine agonists are indicated for the treatment of infertility and pituitary tumours. Cabergoline is preferred because of its efficacy in normalizing prolactin levels and reducing tumour size (Webster et al., 1992). Selective estrogen receptor modulators (SERMs) are compounds that act as agonists or antagonists of estrogen receptors. SERMs such as clomiphene citrate (CC), tamoxifen and toremifene have been used in women to treat breast cancer and osteoporosis, but their use in men for hypogonadism and infertility is currently prohibited. A meta-analysis showed that the use of estrogen antagonists is associated with a significant increase in pregnancy rate, sperm concentration and sperm motility percentage (Chua et al., 2013).

Infertility in men with high levels of reactive oxygen species (ROS) in seminal fluid has been linked to sperm dysfunction and DNA damage. Taking antioxidant supplements has been suggested to improve sperm function and DNA integrity, but most studies are not randomized controlled trials. The benefits of antioxidants may be limited to certain patient groups. Pharmaceutical companies produce and sell specific combinations of antioxidants, but trials have not found significant improvements in sperm parameters or pregnancy rates. A systematic review of 17 randomized trials found that sperm quality or pregnancy rates improved in 82 % of cases after taking antioxidants. However, there are no specific recommendations for the use of antioxidants in the treatment of male infertility and the use of these drugs is purely empirical (Rolf et al., 1999).

It's important to note that the appropriate treatment approach for male infertility depends on the underlying cause, the severity of the condition and individual patient factors. A comprehensive assessment by a healthcare provider specializing in male reproductive health is essential to determine the most appropriate treatment plan for each individual or couple facing infertility. In the search for safer and more accessible treatments, research into phytotherapy offers hope to those struggling with male infertility and highlights the importance of holistic approaches to reproductive health.

The use of plants in the prevention and treatment of male infertility

Traditional and alternative medicine is becoming an increasingly popular way of treating health conditions. This opens up a powerful new potential for traditional and alternative medicine to develop new drug combinations with fewer side effects (Timalsina et al., 2021). Herbal preparations have long been used in the complex treatment of functional sexual disorders. When sexual function is impaired due to neurohumoral disorders, there is a significant decrease in libido with preserved erection and normal ejaculation in some patients and inadequate sexual desire in others. A significant group of sexual disorders is based on mental disorders, often associated with interpersonal relationships between partners and primarily manifested by erectile dysfunction (Miroshnikov, 2005). In the treatment of these conditions, it is necessary to prescribe herbal preparations to suppress anxiety, fear and tension, relieve neurotic reactions and relax the spinal and extraspinal centers of erection and ejaculation. Prescribing these drugs can be useful for increasing the body’s defenses, its immune responses, as well as for eliminating the inflammatory process of the prostate gland and stimulating all components of the copulatory cycle: neurohumoral (libido), mental, erectile, ejaculatory (orgasmic) (Miroshnikov, 2005). Many medicinal plants have attracted attention for their potential role in improving male fertility (Fig. 3).

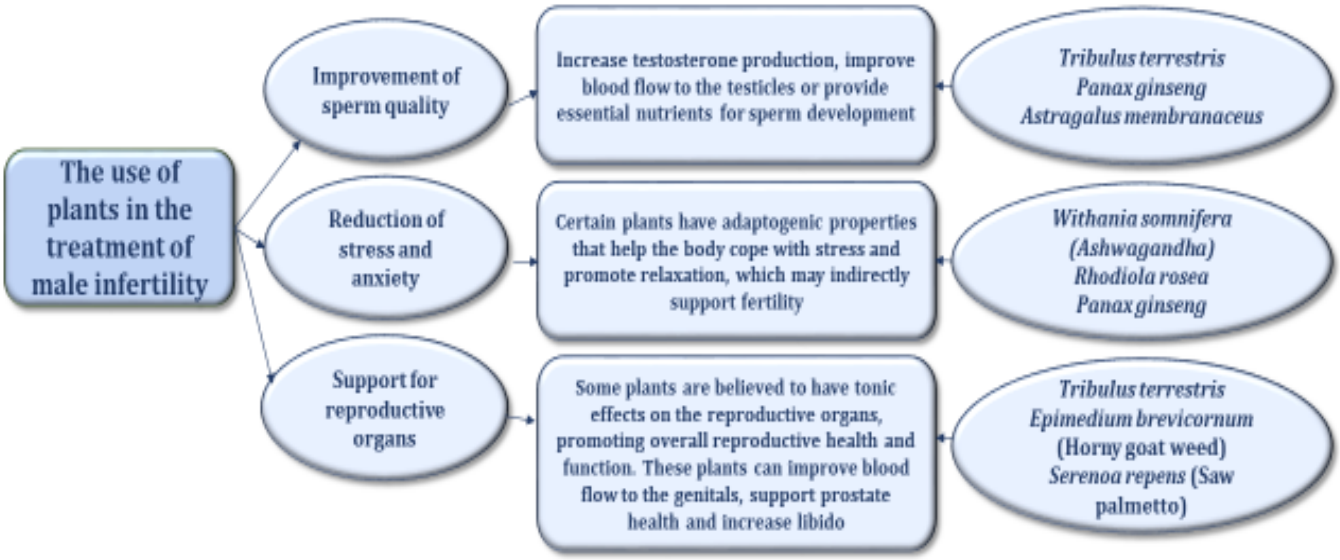

Fig. 3. The use of plants in the treatment of male infertility

It's important to note that while herbs offer potential benefits in the prevention and treatment of male infertility, more research is needed to fully understand their mechanisms of action, efficacy and safety. It's also advisable to consult a healthcare professional before incurporating herbal remedies into a fertility regimen.

Tackweed (Tribulus terrestris L.)

Tribestan, a non-hormonal drug, has been used successfully in clinical practice for 30 years to treat certain forms of male fertility disorders, erectile dysfunction, neurovegetative and neuropsychic manifestations of menopausal and postcastration syndromes, and hypercholesterolaemia (Protich et al., 1983; Dimitrov et al., 1987; Ismail et al., 2014; Spivak et al., 2018). The active ingredient, which contains furastanol-type steroidal saponins, is extracted from the aerial part of the ubiquitous perennial plant *Tribulus terrestris* (Fig. 4). *T. terrestris* is rich in steroidal saponins, particularly protodioscin and its derivatives. These saponins are thought to be responsible for many of the plant's pharmacological effects, including its purported benefits for male fertility. Steroidal saponins are used as raw materials in the manufacture of steroid hormones. The two predominant furastanol bigcosides in *T. terrestris*, protodioscin and protogracilin, have been tested as biologically pure substances. Protodioscin is believed to be metabolised in the body to dehydroepiandrosterone, which has beneficial effects on erectile function, immunity, cell membrane integrity and cholesterol metabolism. Other saponins found in *T. terrestris* extract are thought to modulate the effects of protodioscin (Santos et al., 2019; Sanagoo et al., 2019).

Fig. 4. Perennial plant *Tribulus terrestris* L. (https://podlaskiogrod.pl/)

The therapeutic effects of the drug include increased libido, improved quality of erections, increased sperm count and motility, increased serum levels of certain hormones and reduced blood cholesterol levels. Clinical studies have investigated the efficacy of Tribestan in the treatment of oligoasthenozoospermia. Ejaculate volume was within normal limits in all patients before treatment. It did not change after treatment with Tribestan. After treatment with this drug, there was an increase in the number of sperm in 1 ml of semen (not statistically significant) and an increase in sperm motility (statistically significant). In patients who had undergone surgery for varicocele, treatment with Tribestan led to an increase in sperm motility, and other sperm parameters improved insignificantly. In the third and fourth groups (patients with chronic prostatitis and chronic epididymitis), the researchers did not observe a statistically significant improvement in sperm parameters during Tribestan therapy (Protich et al., 1983).

Tribestan is currently a topical drug for the treatment of certain fertility disorders and sexual dysfunction in men. Tribestan has the most noticeable effect on sperm quality, significantly increasing sperm motility and, to a lesser extent, their number and ejaculate volume. Prescription of the drug leads to improved erection quality and increased libido. Tribestan does not interfere with the physiological mechanisms of hormonal regulation. Long-term experience with the drug and the results of clinical studies show that there is no increase in the concentration of hormones in the blood above physiological norms. Tribestan has no contraindications and is a relatively safe drug - no serious side effects have been observed during its prescription. The undoubted above-mentioned advantages of the drug determine the possibility of its further successful use both independently and as a part of complex therapy (Popov, 2011).

Ashwagandha (Withania somnifera (L.) Dunal)

Ashwagandha (*Withania somnifera*, WS) is one of the most widely used herbal remedies for sexual dysfunction and infertility (Fig. 5).

Fig. 5. Ashwagandha (*Withania somnifera* (L.) Dunal) (https://bananalicious.pl/)

Dried mature roots of WS are widely used as an anti-stress agent, an aphrodisiac, and for the treatment of impotence and infertility (Kulkarni and Dhir, 2008; Ahmad et al., 2010; Mahdi et al., 2011; Durg et al., 2015, 2018). This plant is known to contain more than 80 types of phytochemicals, including steroidal and non-steroidal alkaloids, steroidal lactones and saponins, isopelleterin, anaferin, anagigrin, hygrin, cuscohygrin, tropin, pseudotropin, sonanin, ashwagandha, sophaferines, sonanin, pseudovitanin, somnin, somniferin, somniferinin, 3-tropylthigloate, uanin, uazomin, vis uaferin A and sitoindosides from all these components have been crucial in the treatment of WS (Mishra et al., 2000). The active constituents of WS root extract are steroidal lactones with ergostane, including withanone, withaferin, withanolides, withanolide C, sitoindosides and about 0.2 % alkaloids (Durg et al.,

2015, 2018; Kulkarni and Dhir, 2008, Mirjalili et al., 2009). Extracts of WS fruits, leaves, stems and especially roots improve sperm quality indicators such as motility and quantity in men, and also reduce the effects of chemical toxins on the gonads of men and women. WS can also enhance folliculogenesis and spermatogenesis, improve the balance of LH, FSH and testosterone, and increase gonadal weight in both sexes (Nirupama and Yajurvedi, 2015). In the male reproductive system, WS is thought to promote enzyme activity, alter oxidative stress and prevent cell apoptosis by providing metal ions (Shukla et al., 2011). WS root extracts induce alanine transaminase activity, which increases alanine content in seminal fluid, leading to a decrease in oxidative stress index and improved sperm quality (Gupta et al., 2013).

Experimental studies have shown that an aqueous extract of WS induces testicular development and spermatogenesis in immature Wistar rats and affects seminiferous tubules and folliculogenesis to induce puberty in immature female rats (Al-Qarawi et al., 2000; Abdel-Magied et al., 2001). Oral administration of high concentrations of WS root extract to healthy women has been shown to improve sexual function (Dongre et al., 2015). In addition, WS root extract showed significant activity in the treatment of libido disorders, sexual activity and penile erectile dysfunction in rats (Ilayperuma et al., 2002; Sahin et al., 2016). Clinical studies of WS root extract have demonstrated its activity against psychogenic erectile dysfunction, improvement of sperm count and hormonal profile, and oxidative stress in infertile men (Ahmad et al., 2010; Mahdi et al., 2011; Shukla et al., 2011; Ambiye et al., 2013; Gupta et al., 2013). Bhattarai and colleagues demonstrated that a methanolic extract of WS releases gonadotropin-releasing hormone (GnRH) by acting on gamma-aminobutyric acid (GABA)-A receptors, leading to puberty and fertility in mice (Bhattarai et al., 2010). WS has been shown to improve reproductive function in many ways. WS extract reduced infertility in male subjects by improving semen quality, which was proposed to be due to increased enzymatic activity in seminal plasma and reduced oxidative stress. WS extract also improved LH and FSH balance, leading to folliculogenesis and increased gonadal weight, although some animal studies had concluded that WS had reversible spermicidal and infertilising effects in male subjects (Nasimi Doost Azgomi et al., 2018).

Celeriac (Apium graveolens L.)

Different parts of this plant (Fig. 6) have a wide range of biological, pharmacological and therapeutic effects, including anti-rheumatic, sedative, hypotensive, antifungal, analgesic, anti-inflammatory, detoxifying, antispasmodic, antibacterial, anti-contractile and anti-epileptic (Kooti et al., 2014).

Fig. 6. Celeriac (*Apium graveolens* L.) (https://www.drogadonatury.pl/)

One study showed that celery has a protective effect on the testes against sodium valproate (Hamza and Amin, 2007) and di(2-ethylhexyl) phthalate (Madkour, 2014). Studies have shown that celery protects testes from functional and structural damage and sperm from toxicity induced by atrazine (Abarikwu et al., 2012) and quinine sulphate (Farombi et al., 2012). Kooti and co-workers (2014) investigated the effects of a hydro-alcoholic extract of celery on the histological characteristics of the testes and the number of

sex cells in male rats. There was a significant increase in the number of sperm, Sertoli cells and primary spermatocytes in the groups that received the extract, but no structural changes were observed in the groups. It appears that celery increases spermatogenesis in male rats, but has no destructive effects on testicular tissue (Kooti et al., 2014).

Cornelian cherry (Cornus mas L.)

Cornelian cherry is a fruit-bearing shrub or small tree native to Europe and parts of Asia. It is prized not only for its culinary uses, but also for its potential health benefits. The Cornelian cherry is rich in various antioxidants, including phenolic compounds, flavonoids and anthocyanins. Some studies suggest that the Cornelian cherry may have anti-inflammatory properties, which could help to alleviate inflammation-related conditions such as arthritis and inflammatory bowel disease (Gąstoł et al., 2013; Dinda et al., 2016). In addition, consumption of the Cornelian cherry may have a positive effect on cardiovascular health. The antioxidants found in the fruit may help lower cholesterol levels, thereby reduce blood pressure and improve blood vessel function, reducing the risk of heart disease (Hosseinpour et al., 2017; Szot et al., 2024). The high fibre content of the Cornelian cherry may promote digestive health by supporting regular bowel movements and preventing constipation. It may also have a prebiotic effect, promoting the growth of beneficial gut bacteria (Hosseinpour-Jaghdani et al., 2017; Haghani et al., 2021). Studies have suggested that Cornelian cherry extract may have protective effects on the liver, potentially reducing liver damage caused by toxins or disease (Sangsefidi et al., 2021). Some research suggests that the bioactive compounds in Cornelian cherry may have anticancer properties. These compounds may inhibit the growth of cancer cells and induce apoptosis (programmed cell death) in cancer cells, although more research is needed to confirm these effects (Yousefi et al., 2015; Radbeh et al., 2020). *C. mas* fruit (Fig. 7) is used to treat inflammation, stomach pain and cramps, diarrhoea, various skin infections, intestinal parasites and haemorrhoids (Zarei and Shahrooz, 2019).

Fig. 7. Cornelian cherry (*Cornus mas* L.) (https://cornusmas.eu/)

It was found that *C. mas* fruit extract reduced cellular atrophy by controlling the use of lipid and carbohydrate-based energy substrates *via* provoking the testicular antioxidant status. Cornelian cherry fruit extract, as an antioxidant compound, could reduce cellular degeneration, reduce inflammation and upregulate testicular antioxidant status. Cornelian cherry fruit extract plays a role in reducing oxidative stress by increasing total antioxidant capacity. It can be concluded that this extract may protect the reproductive organs from the side effects of methotrexate, a folic acid antagonist (Zarei et al., 2014).

Satureja khuzistanica Jamzad

Satureja khuzistanica is a plant endemic to the southern part of Iran (Fig. 8).

Its fame is due to its medicinal use as an analgesic and antiseptic in folk medicine, due to the essential oil it contains. Recent studies have shown significant antioxidant, antidiabetic, antihyperlipidemic and reproductive stimulating effects of oral administration of *S. khuzestanica* to rats (Safarnavadeh and Rastegarpanah, 2011).

Fig. 8. *Satureja khuzistanica* Jamzad. (https://uhrohmuh.com/)

Treatment of male Wistar and albino rats with essential oil from aerial parts of *S. khuzestanica* (75, 150, 225 mg/kg/day for 45 days and 225 mg/kg/day for 28 days, orally) resulted in significant improvement in potency, fertility, fertility index and litter size and a significant reduction in post-implantation loss. *S khuzestanica* essential oil protects the reproductive system from cyclophosphamide toxicity through its antioxidant potential and androgenic activity (Haeri et al., 2006; Rezvanfar et al., 2008).

Fineleaf fumitory, fine-leaved fumitory or Indian fumitory (Fumaria parviflora Lam.)

Fumaria parviflora is a herbaceous plant that grows in many parts of Iran, the Indo-Pakistani subcontinent and Turkey (Fig. 9).

Fig. 9. Indian fumitory (*Fumaria parviflora* Lam.) (https://www.maltawildplants.com/)

The aerial parts of *F. parviflora* have been traditionally used in Iranian folk medicine for liver and biliary disorders and dermatological disorders such as scabies, eczema and acne, and as an antiscorbutic, anti-bronchitis, diuretic, expectorant, antipyretic, diaphoretic, appetite stimulant and antineoplastic (Dorostghoal et al., 2014). *F. parviflora* has been shown to have a positive effect on spermatogenesis in male rats (Heydari Nasrabadi et al., 2012). Phytochemical analysis of some plants of the genus *Fumaria* including *F. parviflora* has revealed the presence of isoquinoline alkaloids namely protopine, cryptopine, sinactine, stylopine, bicuculline, adlumine, parfumine, fumariline, fumarophycine, fumaritine, dihydrofumariline, perfumidine and dihydrosanguirine (Suau et al., 2002). The results of Dorostghoal and co-workers (2014) showed that ethanolic extract of *F. parviflora* leaves has the potential to restore reproductive suppression associated with lead exposure and to prevent lead-induced testicular toxicity in male Wistar rats.

Date palm (Phoenix dactylifera L.)

P. dactylifera pollen (Fig. 10) is used as a traditional herbal remedy for male infertility.

Fig. 10. Date palm (*Phoenix dactylifera* L.) (https://www.gardenia.net/)

In ancient times, this pollen was used in traditional Egyptian medicine to improve and restore male fertility (Fallahi et al., 2015; Abdi et al., 2017). In addition, the use of *P. dactylifera* pollen suspension helps to improve sperm count, motility and morphology and also causes a concomitant increase in testicular and epididymal weight. This is because it contains estradiol and flavonoid components that have a positive effect on sperm quality (Malviya et al., 2011). Research has shown that *P. dactylifera* pollen can stimulate the gonads (Ishurd and Kennedy, 2005). Palm pollen increases spermatogenesis and DNA production by improving sperm motility and morphology (Sanocka and Kurpisz, 2004). Palmitic acid and stearic acid found in date palm pollen inhibit the enzyme 5α-reductase, so less testosterone is converted to dihydrotestosterone, which subsequently increases blood testosterone levels (Alvarez et al., 1987).

Nigerian Walnut (Plukenetia conophora Müll.Arg.)

P. conophora (Fig. 11) is a rich source of polyphenols, which are naturally occurring antioxidants that have recently attracted considerable attention for the prevention of oxidative stress-related diseases such as cancer, cardiovascular disease, degenerative diseases and infertility. The antioxidant properties, ROS scavenging and modulation of cellular function of flavonoids account for the majority of their pharmacological activity (Olaniyan et al., 2018). In 2018, Olaniyan et al. (2018) evaluated the effects of *Plukenetia conophora* (PC) and 4H-pyran-4-one 2,3-dihydro-3,5-dihydroxy-6-methyl (DDMP) on Wistar rats with cadmium chloride-induced testicular damage. Significant increases in sperm count, motility and viability were observed in the PC-treated groups. Levels of malondialdehyde (MDA) and nitric oxide were significantly reduced. Significant increases in antioxidant enzymes, proton pump and testosterone were observed in the treated groups.

Fig. 11. Nigerian walnut (*Plukenetia conophora* Müll. Arg.) (https://pfaf.org/)

Other plants

The study by Olaniyan and co-workers (2021) aimed to investigate the effect of *Cocos nucifera* L. oil on lead acetate-induced reproductive toxicity in male Wistar rats. *C. nucifera* oil reduced the adverse effects of lead acetate in male Wistar rats, which may be due to its polyphenol content and antioxidant properties. The role of an aqueous extract of *Adansonia digitata* L. against cadmium chloride-induced testicular damage in Wistar rats was evaluated by Dare and co-workers (2021). The group treated with cadmium chloride plus *A. digitata* caused a significant decrease in MDA levels with a significant increase in antioxidant activity and biochemical enzymes. The aqueous extract of *A. digitata* seems to have a curative effect on cadmium chloride-induced testicular damage. This may be due to the presence of a polyphenolic compound (Dare et al., 2021). *Garcinia kola* Heckel and vitamin E show liver protection against oxygen free radicals produced by lead ions by maintaining the tissue integrity of rat testes (Dare et al., 2014). The use of ginger (*Zingiber officinale* Roscoe) and cinnamon (*Cinnamomum verum* J. Presl) in diabetic rats significantly improved the deleterious effects of oxidative stress on spermatogenesis and fertility parameters compared to ginger and cinnamon alone. It appears that the antioxidant content of herbs can be dramatically increased when used in combination (Khaki et al., 2014). Yamamoto and co-workers (2017) investigated the effects of tomato juice consumption on seminal plasma lycopene levels and sperm parameters in infertile men and found that regular consumption of tomato juice appeared to improve sperm motility in infertile patients. Also, alcoholic extract of *Nigella sativa* L. seeds, especially at higher doses, could increase fertility potential, luteinising hormone (LH) and testosterone concentrations in male rats (Parandin et al., 2012). *Alpinia officinarum* Hance, a traditional medicine, may be effective in improving sperm morphology and sperm count in idiopathic infertility without causing adverse effects (Kolangi et al., 2019). Sadeghzadeh and co-workers (2020) investigated the antioxidant effects of *Ceratonia siliqua* L. extract on ameliorating cyclophosphamide (CP)-induced toxicity on spermatogenesis and showed that *Ceratonia* extract could significantly prevent the adverse effects of CP on sperm motility, mean tissue MDA levels, serum total antioxidants and testosterone.

Africa is renowned for its pharmacologically rich herbs. For many centuries, many African tribes have used herbal infusions to treat and prevent disease, and infertility was no exception. Plants from the families: Fabaceae (16.9 %, 29 species), Euphorbiaceae (7.0 %, 12 species), Asteraceae (5.8 %, 10 species), Apocynaceae, Rubiaceae (5.3 %, 9 species each) and Capparaceae (4.7 %, 8 species). In ethnobotanical studies conducted in Ethiopia (Kareru et al., 2006) and South Africa (Mariuki, 2011), species from these botanical families were recognised as having aphrodisiac and fertility potential. Plants such as *Abrus precatorius* L., *Allium sativum* L., *Cola acuminata* (P. Beauv.) Schott & Endl., *Combretum hereroense* Schinz, *Mondia whitei* (Hook.f.) Skeels, *Plumbago zeylanica* L., *Ricinus communis* L. and *Syzygium guineense* (Willd.) DC. are traditionally used to treat infertility and erectile dysfunction in South Africa, Ghana (Kyarimpa et al., 2023), Cameroon, Guinea and Gabon (Muthee, 2011). Some species (*Cadaba glandulosa* Forssk., *Cadaba farinosa* Forssk., *Combretum illairii* Engl., *Hoslundia opposita* Vahl and *Allophylus pervillei* Blume) have been used to treat both female and male infertility, making them good candidates for further study of their biological activities (Table 1).

Clinical studies on the pharmacological properties of these plants have shown the following results (Tungmunnithum et al., 2018). The *Zingiber officinale* plant showed in a randomised, double-blind, placebo-controlled trial that sperm DNA fragmentation in infertile men was reduced by oral administration of 500 mg/powder for three months. In recent studies, *Whitania somnifera* root, *Alpinia officinarum*, *Nigella sativa* seeds, tomato, *Ceratonia siliqua* capsules, Y virilin, Manix capsules and Tradafertil tablets have shown successful results in the treatment of idiopathic male infertility (Roozbeh et al., 2021). Oral Ashwagandha root has been shown to inhibit lipid peroxidation, improve sperm count and motility, and regulate reproductive hormone levels. However, the molecular mechanisms of these effects have not yet been elucidated (Sengupta et al., 2018). Numerous antioxidants such as vitamin C, vitamin E, glutathione and coenzyme Q10 have also been shown to be effective in treating male infertility (Sinclair, 2000).

Table 1

Most commonly used plant species for the treatment of infertility in men and women in the East African Community countries

Medicinal plants	Parts used	Method of preparation	Route of administration	Treatment group (country)
Spathodea campanulata P.Beauv., is commonly known as the African tulip tree	Bark	Decoction	Oral use	Men (Uganda)
Cadaba glandulosa Forssk.	Roots	Decoction	Oral, half a glass a day for 5 days	Women and men (Kenya)
Cadaba farinosa Forssk.	Roots	Decoction	Oral, half a glass a day for 3 days	Women and men (Kenya)
Combretum illairii Engl.	Root bark	A decoction used with *Grewia tenax* (Forssk.) Fiori for men	Oral, one glass a day for 7 days	Women and men (Kenya)
Hoslundia opposita Vahl	Leaves	Decoction	Oral, 2-3 times a day for 14 days	Women and men (Kenya)
Allophylus pervillei Blume	Roots	Decoction	Oral, one glass a day for 7 days	Women and men (Kenya)

When considering the use of medicinal plants and bioactive phytochemicals in the treatment of male infertility, it's important to evaluate their potential side effects and toxicity. While natural remedies can offer therapeutic benefits, they can also pose risks, especially when taken in large quantities or without proper supervision. Some plants, such as *Abrus precatorius* L. (roots, leaves and seeds), are known to contain highly toxic compounds (abrin, precatorin and hypaphorin). It can be speculated that formulating products using more than one plant or plant part, or with the addition of excipients, may be a way of masking the toxicity of medicinal plants (Kuete, 2018). WS may cause reversible spermicidal and fertilising effects in males and delayed puberty in both sexes; this may be related to the dose, method of preparation, excipients and duration of use (Ilayperuma et al., 2002). Four plants (*Abrus precatorius*, *Catha edulis* (Vahl) Endl., *Cannabis sativa* L. and *Cryptolepis nigrescens* (Wennberg) L.Joubert & Bruyns) are highly toxic and their use may cause adverse effects (Table 2).

Future research should focus on elucidating the underlying mechanisms of action of phytotherapeutic interventions in male infertility. This includes investigating the effects of phytochemicals on sperm production, motility, morphology and fertility, as well as their influence on reproductive hormone levels and signaling pathways. Understanding the molecular mechanisms by which medicinal plants exert their effects will provide valuable insights into their potential therapeutic targets and facilitate the development of targeted interventions (Ahmadian et al., 2022). Large-scale, well-designed clinical trials are needed to provide robust evidence on the efficacy and safety of phytotherapy in male infertility. Future studies should use rigorous methods, including randomized controlled trials with adequate sample sizes, placebo controls and long-term follow-up, to evaluate the therapeutic effects of medicinal plants on male reproductive outcomes. In addition, systematic reviews and meta-analyses should be conducted to synthesize existing evidence and inform evidence-based practice in phytotherapeutic interventions for male infertility. Furthermore, the development of personalised treatment approaches is essential to optimize the efficacy of phytotherapy in male infertility. Tailoring herbal remedies to individual patient characteristics, including age, underlying health conditions, genetic predisposition and lifestyle factors, can improve treatment outcomes and

minimize the risk of adverse effects. In addition, integrating phytotherapy with conventional fertility treatments, such as assisted reproductive techniques and lifestyle changes, can provide synergistic benefits and improve overall patient care.

In conclusion, advancing research in phytotherapy for male infertility requires a multifaceted approach that includes mechanistic studies, standardization efforts, clinical trials, personalized medicine strategies and educational initiatives. By addressing these perspectives, we can harness the full potential of medicinal plants as alternative treatments for male infertility and improve the reproductive health outcomes of affected individuals.

Table 2

Toxicological profile of plants with reported efficacy used in the treatment of infertility

Plants	Toxicity reports	References
Abrus precatorius L., commonly known as jequirity bean or rosary pea	The seeds contain abrin and toxalbumin, the lethal dose for humans being 0.1-1 μg/kg. Poisoning is characterised by severe vomiting and abdominal pain, bloody diarrhoea, convulsions, sensory changes with depression of the central nervous system	(Qian et al., 2022)
Onion (*Allium cepa* L.)	Oral administration of extracts to mice at doses of 250 and 500 mg/kg/day for 30-90 days produced no visible signs of toxicity. An oral dose of 30 g/kg/day for 30 days caused hypothermia, tachypnea, tachycardia, piloerection and polyuria in treated mice	(Bastaki et al., 2021; Elattar et al., 2024)
Garlic (*Allium sativum* L.)	Onion extract caused mild changes in mice at a dose of 300 mg/kg, indicating its relative safety	(Rauf et al., 2022)
Hemp (*Cannabis sativa* L.)	Cannabidiol (the main non-psychotropic component of this species) in extracts of this species is potentially toxic by inhibiting hepatic drug metabolism, altering cell viability *in vitro*, reducing fertilisation capacity, and reducing the activity of α-glycoprotein and other drug transporters	(Huestis et al., 2019; Gorelick, 2023)
Khat or qat (*Catha edulis* (Vahl) Endl.)	Raw khat can damage the liver and kidneys, altering levels of liver enzymes, urea, creatinine and electrolytes needed for liver and kidney function	(Al-Hebshi and Skaug, 2005; Engidawork, 2017)
Kigelia africana (Lam.) Benth., commonly known as sausage tree	Low to moderate toxicity	(Bello et al., 2016)
Sesame, also called benne or gingelly	The ethanolic extract showed low toxicity at a concentration of 500 mg/kg body weight	(Mili et al., 2021)
Ginger (*Zingiber officinale Roscoe*)	The extract was not toxic at a concentration of 5,000 mg/kg body weight	(Gholami-Ahangaran et al., 2021)

Conclusions

Male infertility is a significant challenge to reproductive health and requires the exploration of alternative therapeutic approaches beyond conventional treatments. This review has provided insights into the potential role of phytotherapy in the treatment of male infertility.

The available evidence suggests that phytotherapy is a promising natural complementary therapy for male infertility. Studies have reported beneficial effects of some herbal

supplements on sperm quality, reproductive hormone levels, semen parameters and fertility outcomes in men with infertility. In addition, medicinal plants and bioactive phytochemicals have shown potential for improving male reproductive health through various mechanisms of action.

The growing body of research highlights the need for continued investigation of phytotherapy as a complementary approach to the management of male infertility. Future studies should focus on conducting well-designed clinical trials with larger sample sizes, standardized protocols and longer follow-up periods to determine the efficacy, safety and optimal dosing regimens of phytotherapeutic interventions.

In conclusion, while phytotherapy shows promise as an alternative treatment for male infertility, more rigorous research is needed to validate its clinical utility and elucidate its mechanisms of action. Collaboration between researchers, healthcare providers and traditional practitioners is essential to improve our understanding of phytotherapeutic interventions and optimise their integration into comprehensive fertility care protocols.

Заява інституційної ревізійної ради / Institutional Review Board Statement

Не застосовується / Not applicable.

Заява про інформовану згоду / Informed Consent Statement

Не застосовується / Not applicable.

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