Research progress on the application of the main components of Cuscuta sinensis in the urogenital system

Yue Che¹, Jing-Yu Guo¹, Dong Wang¹, Kang Song¹, Shi-Lin Ding ᵇ

¹First School of Clinical Medicine, Yunnan University of Traditional Chinese Medicine, Kunming 650051, China. ²Department of Urology, The First Affiliated Hospital of Yunnan University of Traditional Chinese Medicine, Kunming 650021, China.

*Corresponding to: Shi-Lin Ding, Department of Urology, The First Affiliated Hospital of Yunnan University of Traditional Chinese Medicine, No. 120, Guanghua Street, Wuhua District, Kunming 650021, China. E-mail: dingshilinde@sina.com.

Author contributions
Yue Che and Jing-Yu Guo conceived this study and drafted the manuscript. Dong Wang and Kang Song located and screened references and critically reviewed articles. Shi-Lin Ding reviewed the article critically. All authors read and approved the final manuscript.

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Abbreviations
PCOS, polycystic ovarian syndrome; TFSC, total flavonoids from semen cuscutae; LH, luteinizing hormone; FSH, folliculogenic hormone; POF, premature ovarian failure; ROS, reactive oxygen species; EVT, extravillous trophoblast; ED, erectile dysfunction; cGMP, cyclic guanosine monophosphate; cAMP, cyclic adenosine monophosphate.

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Abstract
Cuscuta sinensis is a traditional Chinese medicine commonly used in traditional medicine, known for its liver and kidney tonifying effects, sperm fixing and urine reduction properties, fetus calming abilities, eye brightening qualities, and diarrhea stopping capabilities. Modern pharmacological studies have focused on its chemical components such as flavonoids, polysaccharides, alkaloids, steroids, and other bioactive compounds. These studies have revealed its various pharmacological effects, including hormone secretion regulation, ovulation promotion, sperm protection, testicular development promotion, and sperm formation. It is extensively utilized in the treatment of urological and reproductive system diseases, such as male sexual dysfunction, polycystic ovary syndrome, premature ovarian failure, weak spermatozoa, and infertility. This article provides a review of recent advancements in the application of Cuscuta sinensis in the genitourinary system, aiming to enhance the clinical application of Cuscuta sinensis preparations.

Keywords: Cuscuta sinensis; active ingredient; genitourinary system; clinical application; review

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Introduction

*Cuscuta chinensis* Lam. is the dried seeds of *Cuscuta australis* R. Br. or *Cuscuta chinensis* Lam. of the family Cucurbitaceae, which is distributed in most parts of China. *Cuscuta chinensis* is pungent, sweet, and neutral; it belongs to the liver, kidney, and spleen meridians, and has the effects of tonicifying the liver and kidney, fixing sperm and reducing urine, calming the fetus, brightening the eyes, and stopping diarrhea. Modern pharmacological studies have found that there are many chemical components in *Cuscuta sinensis*, such as flavonoids, polysaccharides, alkaloids, steroids, etc. Flavonoids (including kaempferol, quercetin, chrysin, astragalin and lignan) are its main pharmacological components [1, 2]. The pharmacological components of *Cuscuta sinensis* are complex and have a wide range of biological activities, with pharmacological effects such as regulating hormone secretion, promoting ovulation, protecting spermatooza, and promoting testicular development and sperm formation [3]. The author reviewed the research on the application of the main components of *Cuscuta sinensis* in urological and reproductive system diseases (such as male sexual dysfunction, polycystic ovary syndrome, premature ovarian failure, weak spermatooza, infertility, etc.) in recent years in order to provide reference for the clinical application of *Cuscuta sinensis* preparations.

Polycystic ovarian syndrome (PCOS)

PCOS is a reproductive endocrine metabolic disorder characterized by insulin resistance, persistent ovariary disturbances, and hyperandrogenemia [4]. The prevalence of PCOS in China is approximately 5%–10% [5]. The mechanisms underlying PCOS primarily involve hyper-luteinizing hormone (LH), disorders of glucolipid metabolism, hyperinsulinemia, insulin resistance, hyperandrogenemia, obesity, and abnormal ovarian function. In ancient medicine, there was no specific name for polycystic ovary syndrome, but it was generally classified as “late menstruation” and “amenorhea”. Clinical data has shown that kidney deficiency is the most common type of PCOS, often accompanied by blood deficiency, blood stasis, liver depression, and other conditions [6].

*Cuscuta sinensis* is commonly used in the clinical treatment of PCOS, and its main chemical component, flavonoids, have a pleiotropic effect on hypothalamic-pituitary-gonadal endocrine function, which can regulate the environment of gonadal axis disorder in PCOS patients [7]. We found that total flavonoids from semen cuscuae (TFSC) significantly decreased the ovarian index (total mass of ovaries on both sides (mg/body mass of rats (g))), ureter index (ureter index (mg)/body mass of rats (g))), luteinizing hormone/foliculogenetic hormone (LH/FSH), prolactin (PRL), and insulin secretion, increased progesterone (P) levels, decreased tumor necrosis factor α (TNF-α) levels and insulin-like growth factor I (IGF-I) protein levels in ovarian tissues, and improved endometrial hyperplasia, inflammatory infiltration, and islet histopathy, thereby protecting rats in a DHEA combined with HCG-induced PCOS model. It has also been further found that quercetin, a major component of *Cuscuta*, significantly reduced body weight and ovarian volume, improved insulin resistance in PCOS mice, decreased the high level of PCOS-induced hepatic glucokinase (HK) and hexokinase (GK) activity, and increased PCOS-induced estrogen receptor alpha (ERRa) and glucose transporter protein 4 (GLUT4) gene low expression [8, 9]. Quercetin from *Cuscuta sinensis* increased serum lipocalin levels, decreased blood glucose, insulin, cholesterol, and triglyceride levels, decreased androgen and luteinizing hormone levels in vivo, and improved lipocalin-mediated insulin resistance and abnormal hormone levels in PCOS patients [10]. Therefore, it is speculated that quercetin may be an ideal compound for the treatment of insulin resistance and infertility in PCOS. A network pharmacological study found that quercetin and kaempferol may be the main active components of *Cuscuta sinensis* for the treatment of PCOS and may act through targets such as protein kinase B1 (AKT1), mitogen-activated protein kinase 1 (MAPK1), IL-6, and estrogen receptor 1 (ESR1) on diabetic complications AGE-RAGE signaling pathway, fluid shear stress, atheromatous Sclerosis, and endocrine resistance signaling pathways to exert therapeutic effects, as depicted in Figure 1 [11].

Commonly used clinical formulas containing *Cuscuta sinensis* mainly include Wu ZI Yan Zong Wan, Cistanches Cuscuta Sinensis Wan, Ju Jing Xie Xue Yu Yang, Zuo Gui Wan, and You Gui Wan. Yang Xi, Zhao Chunjing, Sun Yongjian, and He Xiaolin used Wu ZI Yan Zong Wan, Xin Jia Cistanches Cuscuta Sinensis Wan, Zuo Gui Wan, and Yao Gui Wan to treat PCOS with an efficiency of 60%, 90%, 93.1%, and 93.3%, respectively, and all achieved satisfactory results [12–15].

Premature ovarian failure (POF)

POF refers to the phenomenon of ovarian function decline with hypergonadotropic hormones (LH, FSH) and reduced estrogen and inhibit in women before the age of 40 years due to multiple causes [16]. More than 80% of patients have an unclear pathogenesis, with clinical manifestations of amenorrhea, decline in ovarian function, and even infertility [17]. When AKT1 is normally expressed, it can maintain the normal growth and development of primordial follicles and regulate the growth of oocytes. However, when its expression is abnormal, it can cause abnormal growth and development of primordial follicles and accelerate ovarian aging. TP53 is also closely related to apoptosis and proliferation of ovarian granulosa cells. Activation of the Caspase3 system can trigger apoptosis and thus accelerate premature ovarian failure [18]. Premature ovarian failure falls under the category of “amenorrhea”, “infertility” and “blood depletion” in Chinese medicine, with the main pathogenesis being the depletion of kidney water. The treatment mainly focuses on tonifying the kidney and benefitting the essence [19].

Western medicine currently utilizes hormone replacement therapy, while traditional Chinese medicine incorporates *Cuscuta sinensis*, which exhibits phytoestrogen-like activity and can be used in the treatment of POF [20]. Wang Yongxia et al. employed cyclophosphamide combined with baixuan to create a rat model of premature ovarian failure [21]. They discovered that TFSF could significantly increase the number of growing follicles, improve ovarian quality, elevate serum estrogen levels, stimulate follicle development in ovaries, and restore the motility cycle in rats, with the high-dose group showing particularly notable effects. The study demonstrated that TFSF had a significant restorative effect on ovarian function in rats with premature ovarian failure. A network pharmacological study revealed that quercetin and kaempferol, the pharmacological components of *Cuscuta sinensis*, may regulate key targets such as AKT1, tumor suppressor protein 53 (TP53), and cstatine3 3 (Caspase3), thus potentially playing a role in the treatment of premature ovarian failure, as depicted in Figure 2. Liu Yanmei, Zhang Xiaoying, and Wu Yan utilized Wu Zi Yan Zong Wan, Jia Wei Zuo Gui Wan, and You Gui Wan to treat patients with premature ovarian failure, yielding remarkable efficiency rates of 96.15%, 91.30%, and 90.00% [18, 22–24].

![Figure 1](https://www.tmrjournals.com/pr)

**Figure 1** Clinical manifestations and physiological mechanisms of polycystic ovarian syndrome (PCOS), physiological mechanisms of the therapeutic effect of changes in the main active ingredients of *Cuscuta sinensis* on PCOS.
Weak spermatozoa and infertility

The incidence of infertility caused by decreased sperm quality has significantly increased in the past few decades, with male factors accounting for 40% of infertile couples in China [25]. Sperm morphology and viability are associated with male fertility, and defects in spermogenesis (mainly head and interrupted defects) are linked to reduced fertility [26]. Reactive oxygen species (ROS) play a crucial role in their development. Abnormal increases in ROS occur under the influence of certain endogenous and exogenous physicochemical factors (such as environmental pollution, ionizing radiation, toxins, hypoxia, varicose veins of the spermatozoa, high-fat diet, and sedentary lifestyle), disrupting the balance of the redox system and triggering oxidative stress. This, in turn, initiates the Caspase cascade reaction, leading to oxidative damage and apoptosis of sperm cells [27]. According to Chinese medicine, the causes of this disease include congenital deficiency, overwork, internal injuries caused by emotional imbalances, and dietary disorders. The disease is primarily located in the kidney, liver, spleen, and sperm chamber, with kidney deficiency accompanied by dampness, stagnation, and stagnation as the main pathogenesis [28].

The Chinese herb Cuscuta has the ability to tonify the kidney, fix the essence, reduce urine, and exhibit antioxidant activity. Several studies have discovered that the aqueous extract of Cuscuta sinensis has protective effects on sperm ultrastructural damage caused by reactive oxygen species [29, 30]. Omirinde JO et al. utilized a rat low protein energy (LP) diet to establish a rat model of testicular dysfunction and observed that Cuscuta sinensis extract significantly decreased the total abnormal sperm count, the number of headless and headless spermatozoa, and the percentage of headless spermatozoa [31]. Additionally, the percentages of headless and headless spermatozoa were significantly reduced. This demonstrated that Cuscuta sinensis extract enhanced the morphology and characteristics of spermatozoa in male rats. Meng et al. established a rat model of oligozoospermia using cyclophosphamide and demonstrated that Cuscuta flavonoids significantly increased the number and motility of spermatozoa in epididymal fluid, increased the number of spermaticogen cells, and improved the morphology of testes, spermaticogen tubules, and spermaticogen cells [32]. Fas and FasL are considered lethal genes, and their abnormal expression can trigger the caspase family cascade reaction, leading to apoptosis of germ cells. Some scholars discovered that TFSC significantly improved sperm quality, promoted testosterone secretion, increased the activity of intra-testicular marker enzymes such as acid phosphatase (ACP), lactate dehydrogenase (LDH), and succinate dehydrogenase (SDH), decreased lipid peroxide (MDA) content, increased the levels of GSH and T-SOD (indicators of antioxidant activity), and down-regulated the gene expression of Fas and FasL. This indicates that TFSC could treat oligozoospermia by inhibiting oxidative stress and downregulating the expression of apoptotic genes Fas and FasL, as depicted in Figure 3 [33]. Huang Wenhui, Yang Yongjun, Wang Dingguo, Sun Song, and He Xueyou utilized Wu Zi Yan Zong Wan, Cistanches Cuscuta Sinensis San, Ju Jing Xie Xue Yu Tang, Zuo Gui Wan, and You Gui Wan to treat patients with weak spermatozoa and observed significant improvements in sperm motility and density, with notable advantages [34–38].

Infertility

Infertility is a prevalent and challenging condition in gynecology, with ovulation disorders being a primary cause. Ovulation disorders encompass anovulation, abnormal ovulation, and luteal failure. The etiology and pathogenesis of these disorders are highly intricate, primarily involving dysfunction in the hypothalamic and pituitary glands, ovarian abnormalities, and endocrine metabolic disorders. Treating this condition clinically is also arduous, but Chinese medicine offers distinct advantages in its management. According to Chinese medicine, this condition arises from dysfunction in the kidney-tiankui-hypophyse-uterine reproductive axis.

Cuscuta sinensis is a commonly used medication in the clinical treatment of infertility. Research has indicated that Cuscuta flavonoids have effects on reproductive endocrine systems in both female and male rats [39]. Zhu et al. utilized hydroxyurea to establish a rat model of renal deficiency ovulation disorder and demonstrated that Cuscuta flavonoids increased body weight, uterine index, follicle number, mature follicle ratio (maturation/follicles/totals follicles), as well as serum levels of E2, FSH, and LH in experimental rats [40]. These experiments confirmed the significant therapeutic effects of Cuscuta flavonoids on all rats with the renal deficiency ovulation disorder model. Luo Keyan et al. discovered that Cuscuta flavonoids notably improved the overall condition of rats with ovulatory disorders, enhanced uterine and ovarian indices, promoted follicle growth and development, increased the number of secondary follicles, and restored the motility cycle of rats [41]. The high dose of Cuscuta flavonoid exhibited even more significant effects, leading to the conclusion that Cuscuta flavonoid has a substantial impact on ovulatory disorders. In another study, Luo Keyan et al. found that Cuscuta flavonoids also significantly improved the levels of sex hormones in the hypothalamic-pituitary-ovarian (HPO) axis in rats with ovulatory disorders, as depicted in Figure 4 [42].
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Cryptorchidism

Cryptorchidism is a prevalent congenital disorder affecting the male reproductive system. It is commonly observed in male infants born at full term, with the incidence decreasing with age. It is also a significant contributing factor to male infertility [45]. Dysfunction in the hypothalamic-pituitary-gonadal axis, abnormal anatomy, androgen receptor abnormalities, as well as genetic and physicochemical factors, play crucial roles in the development of cryptorchidism and impairment of testicular function [46]. Furthermore, in cases of unilateral cryptorchidism, where the testes fail to descend into the scrotum in a timely manner, the elevated intra-testicular temperature leads to changes in testicular supporting cells, interstitial cells, and spermatogenic cells, ultimately affecting fertility [47]. Hornakova et al. also discovered that unilateral cryptorchidism results in damage to the contralateral testis, leading to infertility [48]. Qin et al. immobilized the right testis by severing the right testicular lead [49]. The results demonstrated that the administration of Cuscuta sinensis extract increased the weight of the contralateral testis, reduced testicular spermatogenic cell apoptosis, increased mitochondrial membrane potential, decreased ROS levels, MDA content, and cleaved caspase-3 expression. These findings suggest that Cuscuta sinensis extract may have a potent antagonistic effect on unilateral cryptorchidism by downregulating the apoptosis of contralateral testicular spermatogenic cells induced by unilateral cryptorchidism, as depicted in Figure 5.

Abortion

Abortion is a prevalent disorder that occurs during pregnancy, and its exact pathogenesis remains unknown. Successful embryo implantation is a critical factor in ensuring a successful pregnancy, with the proper invasion of extravillous trophoblast (EVT) cells playing a crucial role in this process. Dysfunction of these cells has been suggested as a major cause of miscarriage. Maintaining the homeostasis of matrix metalloproteinase 9 (MMP9) is vital in regulating the invasion of EVT cells [50]. The normal expression and function of the endometrium during the implantation phase are of utmost importance in establishing and maintaining pregnancy, as well as initiating labor. The Notch signaling pathway, AKT signaling pathway, and MAPK signaling pathway are involved in various physiological and pathological processes, including cell growth, development, differentiation, and apoptosis. These pathways are essential for the invasion and proliferation of endometrial stromal cells and trophoblast cells, which are crucial for successful implantation [51]. Through a meta-analysis, Zhang Wenwen identified Cuscuta sinensis as the most commonly used remedy for recurrent miscarriage, particularly in tonifying the kidney and activating blood to warm kidney yang [51].

TFSC has previously been utilized in clinical settings for the prevention or treatment of miscarriage. Gao Feixia et al. employed wound healing and transwell assays to examine the migration and invasion functions of human chorionic trophoblast cells [52]. They also analyzed the regulatory effects of TFSC on MMP9 expression and related signaling pathways through Western Blot. The findings indicated that TFSC effectively enhanced the migration of EVT cells in a dose- and time-dependent manner. Additionally, it significantly increased the expression of MMP9 in EVT cells and up-regulated the protein expression in Notch, AKT, and p38/MAPK signaling pathways. Notably, a significant effect was observed in spontaneous abortion. High-dose TFSC significantly up-regulated the expression of estrogen receptor (ER), progesterone receptor (PBR), and prolactin receptor (PRLR) in metaphase tissues. These findings indicated that TFSC could exert its anti-abortion effect by interfering with the MAPK signaling pathway, as depicted in Figure 6. Zhao Fanqin et al. employed Zuo Gui Wan in combination with Zuo Yao Wan to treat habitual abortion [54]. They discovered that the pregnancy rate after treatment reached 88.69%, which improved embryo implantation and viability.

Erectile dysfunction (ED)

ED is a prevalent male urological condition characterized by the persistent inability to achieve or maintain an erection for satisfactory sexual performance [55]. It affects approximately 150 million men worldwide. The failure of penile erection can be attributed to impaired relaxation of smooth muscles within the penile corpus cavernosum. This impairment is mediated by intracellular second messengers, namely cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP). Activation of cGMP/cAMP-specific protein kinases leads to the opening of K⁺ channels and closure of Ca²⁺ channels, resulting in smooth muscle relaxation [56, 57]. Consequently, drugs that inhibit the hydrolysis of cGMP/cAMP have the potential to increase cyclic nucleotide signaling, thereby enhancing smooth muscle relaxation in the penile corpus cavernosum and promoting penile erection.

Cuscuta, a commonly used herbal medicine in urological male medicine for ED, is known for its ability to nourish the liver and kidney and improve sexual function. Sun et al. conducted a study using phentolamine to pretreat healthy male rabbits and obtain penises [58]. The findings revealed that Cuscuta extract significantly increased the levels of cGMP and cAMP in the penile corpus cavernosum. Additionally, it significantly enhanced the diastole of the penile corpus cavernosum induced by sildenafil. This study demonstrated that Cuscuta seed extract exerts a diastolic effect on penile cavernous tissue, partially through the activation of the NO-cGMP pathway. It suggests that Cuscuta seed extract may improve erectile dysfunction in cases where the response to sildenafil is incomplete, as depicted in Figure 7. Wang M. B. et al. utilized Cuscuta seed-containing Semen Promoter Capsules and Wuzi Yanzong Pill to treat impotent patients, achieving a total effective rate of 91.8% and 68.9% respectively, with significant clinical outcomes [59].

Figure 5 Endogenous and exogenous physicochemical factors and physiological mechanisms of cryptorchidism and the physiological mechanisms by which changes in the main active components of Cuscuta sinensis exert their therapeutic effects on cryptorchidism.
Cuscuta sinensis is a significant medicine used for warming kidney yang. It is widely distributed throughout the country, with major production areas in Shandong, Inner Mongolia, Gansu, Hebei, Anhui, and other regions. It has a high yield and minimal side effects. The primary chemical components of Cuscuta sinensis include flavonoids, polysaccharides, alkaloids, terpenoids, steroids, volatile oils, and lignans. Among these, flavonoids are the main medicinal constituents of Cuscuta sinensis, including chrysoside, isoqueritin, zingiberin, quercetin, kaempferol, isorhamnetin, and others. Modern research indicates that flavonoids, as the primary component of Cuscuta sinensis, can potentially regulate hormone levels, exhibit antioxidant properties, and inhibit apoptosis of spermatogenic cells. These mechanisms help counteract damage to the genitourinary system caused by endocrine disorders and oxidative stress. Consequently, Cuscuta sinensis flavonoids hold medicinal potential for treating various genitourinary system diseases such as infertility, decreased sexual function, and oligosperma as depicted in Supplementary Table 1. Furthermore, the use of cyberpharmacological tools allows for extensive prediction of additional active ingredients, targets of action, and potential therapeutic directions [60]. Research on Cuscuta sinensis in the genitourinary system has shown improvement in recent years, although there are still some challenges in clinical practice applications. Additionally, Cuscuta sinensis has demonstrated immunological, cardiovascular, antioxidant, and anti-aging effects. However, relatively few studies have been conducted in these areas in recent years [61]. Therefore, Cuscuta sinensis holds great prospects for development and exploration in terms of its pharmacological effects and clinical applications.

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